UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: 1/06/2010

SUBJECT: **Abamectin:** Review of developmental neurotoxicity study (MRID 47116201, 2007 study)

PC Code: 122804
Decision No.: NA
Petition No.: NA
Risk Assessment Type:NA
TXR No.: 0054615
MRID No.: 47116201

DP Barcode: 339800
Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: NA
40 CFR: NA

FROM: Whang Phang, PhD
Toxicologist
RAB /HED (P7509P)

THROUGH: Paula Deschamp, Branch Chief
RAB /HED (P7509P)

TO: Thomas Harris, Risk Manager Review
Risk Management Team 07
RD (P7509P)

ACTION REQUESTED: Review the second developmental neurotoxicity study in rats on abamectin (MRID 47116201).

RESULTS and DISCUSSION: The second developmental neurotoxicity study on abamectin in rats has been reviewed and the results and conclusion are presented below.

In a developmental neurotoxicity study (MRID 47116201), Abamectin (96.2% a.i. on dry basis; Batch No.: VS094KO) in sesame oil was administered via gavage (10 mL/kg) to pregnant Alpk:AP$_f$SD rats (30/dose) from gestation day (GD) 7 through lactation day (LD) 22 at doses of 0, 0.12, 0.20, or 0.40 mg/kg/day. The pups were not directly dosed. Dams were allowed to

deliver naturally and were killed on LD 29. On post-natal day (PND) 5, litters were standardized to 8 pups/litter; the remaining offspring were sacrificed and not examined further. Subsequently, 1 pup/sex/litter/group (at least 10 pups/sex/dose when available) were allocated to the following subsets: Subset 1: functional observational battery (FOB) on PND 5, 12, 22, 36, 46, and 61; motor activity on PND 14, 18, 22, and 60; and brain weight and neuropathology on PND 63. Subset 2: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 24 and 27; and brain weight and neuropathology on PND 63. Subset 3: FOB on PND 5 and 12; auditory startle on PND 23 and 61 (for animals not sacrificed on PND 12); and brain weight and neuropathology on PND 12. Subset 4: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 59 and 62.

Maternal toxicity: There were no effects of treatment on mortality, clinical signs, functional observational battery parameters, body weights, body weight gains, food consumption, reproductive performance, or gestation length.

The maternal LOAEL was not observed. The maternal NOAEL is 0.4 mg/kg/day.

Offspring toxicity: Following culling on PND 5, mortality and associated clinical signs of toxicity were observed in the 0.40 mg/kg/day pups. A total of 32 males and 27 females were missing and presumed dead, found dead, or killed for humane reasons or due to clinical signs of toxicity. The pups were generally small in size and presented with dehydration (133-151 observations in 42-45 pups) and tremors (276-292 observations in 66-67 pups). Additionally at this dose, pup body weights were decreased ($p<=0.05$) by 10-36% compared to controls from PND 8 to 36. There were no surviving pups at this dose level after PND 38. Since these deaths left an insufficient number of pups to complete all of the study objectives, all dams and pups at this dose were removed from the study during PND 15-38.

No treatment-related effects were observed on litter parameters (number born live, number born dead, sex ratio (% male), mean litter size, live birth index, and viability index), clinical signs, FOB parameters, motor activity, auditory startle reflex, learning and memory, sexual maturation, brain weight, or gross or microscopic pathology in the 0.12 or 0.2 mg/kg/day groups.

Decreases ($p\leq0.05$) in post-weaning body weight were observed in the 0.12, 0.20, and 0.4 mg/kg/day males throughout the post-weaning interval (PND 36-63). The individual pup body weight data were re-evaluated using Mixed Model Analysis of Body Weight Data from Developmental Neurotoxicity Study. The results indicated that there was a statistically significant difference for mid- and low-dose males from the corresponding controls, and for females no statistical significant difference existed. However, the decrease in low-dose males was approximately 3% relative to the controls, and it was determined not to be toxicologically significant. **The offspring LOAEL for this effect is established at 0.2 mg/kg/day based on statistically and biologically significant body weight reductions (6%). The NOAEL for this effect is established at 0.12 mg/kg/day.**

This study is acceptable/non-guideline.

MRID Summary Table

Study Type	MRID	Comments
developmental neurotoxicity study in rats	47116201	The study is classified as acceptable non-guideline

DATA EVALUATION RECORD

ABAMECTIN

Study Type: OPPTS 870 6300 [§83-6], Developmental Neurotoxicity Study in Rats

Work Assignment No. 4-1-145 (MRID 47116201)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Bldg 100, Ste B
Durham, NC 27713

Primary Reviewer
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 7/9/07

Secondary Reviewer
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 7/9/07

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 7/9/07

Quality Assurance:
Mary Menetrez, Ph.D.

Signature: Mary X Menetrez
Date: 7/9/07

Disclaimer

This Data Evaluation Record my have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel

EPA Reviewer: Whang Phang, PhD **Signature:**
Toxicology Branch, Health Effects Division (7509P) **Date:** 10/29/2009
Work Assignment Manager: P.V. Shah for **Signature:**
Registration Action Branch 1, Health Effects Division (7509P) **Date:** 10/2/09

DATA EVALUATION RECORD

STUDY TYPE: Developmental Neurotoxicity Study - Rat; OPPTS 870.6300 (§83-6); OECD 426 (draft)

PC CODE: 122804 **DP BARCODE:** D339800
TXR#: 0054615

TEST MATERIAL (PURITY): Abamectin technical (96.2% on a dry basis)

SYNONYMS: AVID EC, Abamectin, Abamectinum *et al.*

CITATION: Moxon, M.E. (2007) Abamectin: Assessment of developmental neurotoxicity in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Project Id.: CTL Study No. RR1086, Syngenta No. T000516-07, February 20, 2007. MRID 47116201. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 47116201), Abamectin (96.2% a.i. on dry basis; Batch No.: VS094KO) in sesame oil was administered via gavage (10 mL/kg) to pregnant Alpk:AP$_f$SD rats (30/dose) from gestation day (GD) 7 through lactation day (LD) 22 at doses of 0, 0.12, 0.20, or 0.40 mg/kg/day. The pups were not directly dosed. Dams were allowed to deliver naturally and were killed on LD 29. On post-natal day (PND) 5, litters were standardized to 8 pups/litter; the remaining offspring were sacrificed and not examined further. Subsequently, 1 pup/sex/litter/group (at least 10 pups/sex/dose when available) were allocated to the following subsets: Subset 1: functional observational battery (FOB) on PND 5, 12, 22, 36, 46, and 61; motor activity on PND 14, 18, 22, and 60; and brain weight and neuropathology on PND 63. Subset 2: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 24 and 27; and brain weight and neuropathology on PND 63. Subset 3: FOB on PND 5 and 12; auditory startle on PND 23 and 61 (for animals not sacrificed on PND 12); and brain weight and neuropathology on PND 12. Subset 4: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 59 and 62.

Maternal toxicity: There were no effects of treatment on mortality, clinical signs, functional observational battery parameters, body weights, body weight gains, food consumption, reproductive performance, or gestation length.

The maternal LOAEL was not observed. The maternal NOAEL is 0.4 mg/kg/day.

Offspring toxicity: Following culling on PND 5, mortality and associated clinical signs of toxicity were observed in the 0.40 mg/kg/day pups. A total of 32 males and 27 females were missing and presumed dead, found dead, or killed for humane reasons or due to clinical signs of toxicity. The pups were generally small in size and presented with dehydration (133-151 observations in 42-45 pups) and tremors (276-292 observations in 66-67 pups). Additionally at this dose, pup body weights were decreased ($p<=0.05$) by 10-36% compared to controls from PND 8 to 36. There were no surviving pups at this dose level after PND 38. Since these deaths left an insufficient number of pups to complete all of the study objectives, all dams and pups at this dose were removed from the study during PND 15-38.

No treatment-related effects were observed on litter parameters (number born live, number born dead, sex ratio (% male), mean litter size, live birth index, and viability index), clinical signs, FOB parameters, motor activity, auditory startle reflex, learning and memory, sexual maturation, brain weight, or gross or microscopic pathology in the 0.12 or 0.2 mg/kg/day groups.

Decreases ($p\leq0.05$) in post-weaning body weight were observed in the 0.12, 0.20, and 0.4 mg/kg/day males throughout the post-weaning interval (PND 36-63). The individual pup body weight data were re-evaluated using Mixed Model Analysis of Body Weight Data from Developmental Neurotoxicity Study. The results indicated that there was a statistically significant difference for mid- and low-dose males from the corresponding controls, and for females no statistical significant difference existed. However, the decrease in low-dose males was approximately 3% relative to the controls, and it was determined not to be toxicologically significant. **The offspring LOAEL for this effect is established at 0.2 mg/kg/day based on statistically and biologically significant body weight reductions (6%). The NOAEL for this effect is established at 0.12 mg/kg/day.**

This study is acceptable/non-guideline.

COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, Flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Abamectin technical (a mixture of ≥80% Avermectin B1a and B1b)

Description: White powder

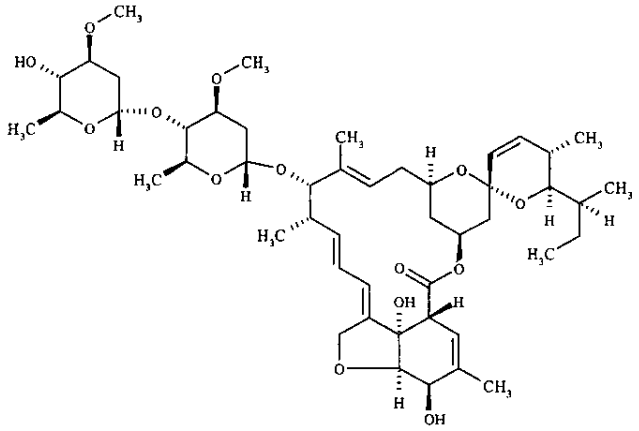
Batch No.: VS094KO

Purity: 96.2% on a dry basis

Stability of compound: It was stated that stability of the test material in the vehicle was determined in another study; however, the results were not provided.

CAS #: 71751-41-2

Structure:



2. Vehicle: Sesame oil

3. Test animals

Species: Rat

Strain: Alpk:AP$_f$SD (Wistar-derived)

Age and weight at initiation of treatment: Females 9-13 weeks of age weighing 226-316 g

Source: AstraZeneca Biological Services Section, Alderley Park, Macclesfield, Cheshire, UK

Housing: Parent females and litters were housed until weaning in solid plastic cages. On PND 29, the selected F1 rats were housed by sex and litter in wire mesh cages.

Diet: CT1 diet (Special Diet Services Limited, Stepfield, Witham, Essex, UK) , *ad libitum*

Water: Tap water, *ad libitum*

Environmental conditions:

Temperature: 22±3°C

Humidity: 30-70%

Air changes: At least 15/hr

Photoperiod: 12 hrs light/12 hrs dark

Acclimation period: 6 days

B. STUDY DESIGN

1. **In-life dates:** Start: Not reported End: Not reported

2. **Study schedule:** The P females were administered the test substance daily via gavage (10 mL/kg) from gestation day (GD) 7 until lactation day (LD) 22 (inclusive). The pups were not directly dosed. On post-natal day (PND) 5, the litters were standardized to 8 pups/litter (with equal sexes where possible) to reduce the variability. Litters of 7 or 8 pups with at least 3 pups of each sex became the F1 generation. Litters that were not selected for the F1 generation were killed and discarded on PND 5. The dams were killed at weaning (PND 29) and were discarded. One F1 rat/sex/litter was killed on PND 12 and PND 63, and their brains were fixed and weighed. At least 10 rats/sex/dose were killed on PND 63, brain weights were measured, and tissues were taken for microscopic analysis. All remaining pups were killed and discarded at PND 63.

3. **Mating procedure:** The animals were time mated by the supplier. The day on which sperm was detected in a vaginal smear was designated as GD 1, and these females were delivered to the testing laboratory. Twenty females were supplied on each of 6 days. Further details were not provided. The day on which parturition occurred was designated as LD 1. Parent females and litters were housed together in solid plastic cages until weaning. The selected F1 rats were then housed by sex and litter in wire mesh cages.

4. **Animal assignment:** Pregnant females were randomly assigned to dose groups as indicated in Table 1. Dams were assigned to functional observation testing as shown. Pups that were not selected for the F1 group, animals found dead, and animals requiring euthanasia were killed and discarded without examination. Offspring were assigned to testing subgroups at the time of litter standardization on PND 5. Animals were allocated to the following subsets (1 pup/sex/litter): Subset 1: functional observational battery (FOB) on PND 5, 12, 22, 36, 46, and 61; motor activity on PND 14, 18, 22, and 60; and brain weight and neuropathology on PND 63. Subset 2: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 24 and 27; and brain weight and neuropathology on PND 63. Subset 3: FOB on PND 5 and 12; auditory startle on PND 23 and 61 (for animals not sacrificed on PND 12); and brain weight and neuropathology on PND 12. Subset 4: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 59 and 62.

TABLE 1. Study Design [a]

Experimental parameter	Dose (mg/kg/day)				Subset [b]
	0	0.12	0.20	0.40	
Maternal animals					
No. of maternal animals assigned	30	30	30	30	NA
FOB (GD 10 and 17; LD 2 and 9)	30	30	30	30	NA
Offspring					
FOB (PND 5)	10/sex	11/sex	11-12/sex	12/sex	1, 2, 3, 4
FOB (PND 12)	9/sex	9-10/sex	8-10/sex	0[c]	1, 2, 3, 4
FOB (PND 22, 36, and 46)	10/sex	11/sex	11-12/sex	0[c]	1, 2, 4
FOB (PND 61)	8/sex	8-9/sex	9-11/sex	0[c]	1, 2, 4
Motor activity (PND 14, 18, 22, and 60)	9-10/sex	10-11/sex	11-12/sex	0[c]	1
Auditory startle habituation (PND 23 and 61)	9-10/sex	10-11/sex	11-12/sex	0[c]	3
Learning and memory (water maze; PND 24 and 27)	19/sex	22/sex	23/sex	0[c]	2
Learning and memory (water maze; PND 59 and 62)	15-18/sex	20-21/sex	20-21/sex	0[c]	4
Brain weight					
PND 12	10/sex	11/sex	11-12/sex	0[c]	3[d]
PND 63 (perfused and non-perfused)	10/sex	11/sex	11-12/sex	0[c]	1, 2
Neuropathology					
PND 12 (brain only)	10/sex	11/sex	11-12/sex	0[c]	3[d]
PND 63	10/sex	11/sex	11-12/sex	0[c]	1, 2

a Data were obtained from pages 16, 19-24, 39-62, and 87-192 of MRID 47116201. Offspring were selected one male or one female from each litter for use in the FOB, motor activity, auditory startle and water maze tests.

b Selected pups were randomly assigned numbers. The first (lowest number) male and female from each litter were assigned to Subset 1. The second male and female from each litter was assigned to Subset 2, and so on.

c As an insufficient number of litters/pups were available to meet the objectives of the study, all dams and pups in the 0.4 mg/kg/day group were removed from the study (PND 15-38 depending in start date).

d Excludes animals selected for auditory startle habituation.

5. **Dose-selection rationale:** The Sponsor stated that the lowest and highest dose concentrations were chosen based on the no observed adverse effect level and the highest dose concentration used in a multigeneration reproduction study (Gordon, 1984). Further information from this study was not provided.

6. **Dosage preparation, administration, and analysis:** All doses were administered once daily to maternal animals by gavage on GD 7 through LD 22 (inclusive). The gavage dose was administered in a volume of 10 mL/kg bw. Dose and volume calculations were based on the body weight of each individual rat, measured daily during the dosing period. Dose formulations were prepared approximately weekly, without adjustment for purity, by mixing appropriate amounts of the test compound in sesame oil to yield the highest concentration, The lower concentrations were prepared by serial dilution. Dose formulations were stored at room temperature. The first, second, and last batches of the dose formulations were analyzed for concentration. The lowest and highest concentrations of the first and second batches were analyzed for homogeneity (top, middle, bottom). It was stated that the chemical stability of abamectin in sesame oil at concentrations of 0.01 mg/mL and 1 mg/mL at room temperature was established in another study (Hollis, 2005); however, the results were not reported.

Results:

Homogeneity (range as % deviation): -4.9 to 7.1%

Concentration (range as % of nominal):

Concentration (mg/mL)	% of nominal
0.012	108.3-116.7
0.02	105.0-115.0
0.04	95.0-100.0

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

C. OBSERVATIONS

1. In-life observations

a. Maternal animals: The dams were checked for mortality twice daily. Clinical observations of the dams were conducted cage-side during acclimation and twice daily during the study. Detailed observations were recorded on GD 1, prior to dosing on GD 7 through LD 22, LD 29, and prior to termination.

On GD 10 and 17 and LD 2 and 9, all females were observed outside the home cage by a technician who was unaware of each rat's dose group. This observation was performed before dosing the animals. It was not stated if the same technicians observed the animals throughout testing. Severity codes for observations were reported as no abnormalities detected, slight, or present. The following functional observations were reported:

	FUNCTIONAL OBSERVATIONS
X	Signs of autonomic function, including: 1) Ranking of degree of lacrimation and salivation, with range of severity scores from none to severe 2) Presence or absence of piloerection and exophthalamus, 3) Ranking or count of urination and defecation, including polyuria and diarrhea 4) Pupillary function such as constriction of the pupil in response to light, or a measure of pupil size 5) Degree of palpebral closure, e.g., ptosis.
X	Description, incidence, and severity of any convulsions, tremors, or abnormal movements.
X	Description and incidence of posture and gait abnormalities.
X	Description and incidence of any unusual or abnormal behaviors, excessive or repetitive actions (stereotypies), emaciation, dehydration, hypotonia or hypertonia, altered fur appearance, red or crusty deposits around the eyes, nose, or mouth, and any other observations that may facilitate interpretation of the data.

Further details concerning the functional observational battery were not provided.

The body weight of each parent female was recorded on GD 1, immediately prior to dosing on GD 7 through LD 22, LD 29, and prior to termination. Food consumption was

calculated (g/rat/day) for GD 1-7, 7-15, and 15-22, and LD 1-5, 5-8, 8-12, 12-15, 15-18, 18-21, and 21-23.

b. Offspring

1. **Litter observations:** The day of completion of parturition was designated as PND 1. On PND 1 and 5, the sex, weight, and clinical condition of each pup were recorded. Cage-side observations for mortality, morbidity and clinical signs were made at least once daily; the F1 animals were also observed when weighed.

   On PND 5, the litters were standardized to 8 pups/litter (with equal sexes where possible) to reduce the variability. The pups retained in each litter were selected at random from litters of 7-8 pups with at least 3 pups of each sex. Pups that were not selected for the F1 generation were killed and discarded. Body weights were recorded on PND 1, 5 (pre-cull), 5 (post-cull), 8, 12, 15, 22 and 29.

2. **Developmental landmarks:** Beginning on PND 41, all male offspring were examined daily for preputial separation. Beginning on PND 29, all female offspring were examined daily for vaginal patency. The age of onset was recorded, and body weights were recorded for each rat on the day of sexual maturation.

3. **Post-weaning observations:** After weaning on PND 29, cage-side observations for mortality, morbidity and clinical signs were made at least once daily, and also when the animals were weighed. Body weights were recorded on PND 36, 43, 50, and 57, at sexual maturation, and at termination.

4. **Neurobehavioral evaluations:** Observations and the schedule for those observations are summarized as follows from the report.

i. **Functional observational battery (FOB):** On PND 5 and 12 (all Subsets) and PND 22, 36, 46, and 61 (Subsets 1, 2, and 4), selected animals (one male or female from each litter) were examined outside of the home cage. The same parameters assessed in the maternal FOB were examined in the offspring by an individual who was unaware of each rat's dose group. Additional information was not provided.

ii. **Motor activity testing:** Motor activity measurements were performed on Subset 1 (one male or female from each litter) on PND 14, 18, 22, and 60. Tests were recorded in a separate room (environmental conditions not provided). An automated activity recording apparatus (make and source not provided) recorded small and large movements as an activity count. Each assessment was divided in into 10 scans of 5 minute duration. Treatment groups were counterbalanced across cage/device number. When trials were repeated, each animal was returned to the same activity monitor. Further details were not provided.

iii. **Auditory startle reflex habituation:** Auditory startle response and habituation testing was performed on Subset 3 (one male or female from each litter) on PND 23 and 61. An

automated system (make and source not provided) was used to measure the mean response amplitude and time to maximum amplitude within each block of 10 trials. There were 5 blocks of 10 trials per session on each day of testing. Further details were not provided.

iv. **Learning and memory testing:** Selected animals (one male or one female from each litter) were tested for associative learning and memory. The test used a "Y"-shaped water maze with one escape ladder. The time taken by the pup to find the escape ladder was recorded for each trial. Animals were given 6 trials on PND 24 (Subset 2) or 59 (Subset 4). Additionally, a straight channel was used to evaluate swimming speed. Each animal completed one trial in the straight channel immediately following the six trials in the "Y"-shaped water maze. Three days later (PND 27 or 62) the same animals were retested using the same procedures. Learning was assessed by comparing the time required to complete the maze on Trial 6 vs Trial 1 in the learning phase. Memory was assessed by comparing the time required to complete the maze in the first trial in the memory phase to the time required in the learning phase. Proportions of successful trials were calculated based on the trial being completed in less than 3, 4, 5, 6, 7, 8, 9, or 10 seconds or 1.0x, 1.5x, or 2.0x the time required to complete the straight channel. Further details were not provided.

5. **Cholinesterase determination:** Cholinesterase activity was not assessed in this study.

6. **Pharmacokinetic data:** Pharmacokinetic data was not evaluated in this study.

7. **Postmortem observations**

a. **Maternal animals:** P females were killed by overexposure to halothane Ph. Eur. vapor followed by exsanguination. Females with litters not required for selection, with total litter loss, and all surviving dams at PND 29 were killed and discarded without examination. Females that failed to litter were examined macroscopically, and the uterus was examined to confirm pregnancy status.

b. **Offspring:** Any animal found dead and the following terminated offspring were not examined pathologically: any pups that required euthanasia, pups not selected for the F1-generation on PND 5, and F1 pups not selected for brain weight measurement.

On PND 12, rats (Subset 3, one male or one female from each litter) were killed by exposure to carbon dioxide, and the brain was immediately exposed and immersion fixed in 10% neutral buffered formol saline. The brains were weighed after approximately 24 hours fixation. The brains from the control, 0.12, and 0.20 mg/kg/day groups were embedded in paraffin wax, sectioned into 7 levels, stained routinely with hematoxylin and eosin, and examined microscopically.

On PND 63, rats (Subsets 1 and 2, one male or one female from each litter) were processed as on PND 12, except that the brain was fixed and stored after weighing. Also, on PND 63, an additional 10 rats/sex/group were deeply anesthetized by intraperitoneal injection of sodium pentobarbitone and killed by perfusion fixation with formol saline. The rats were perfused with a volume of fixative approximately equivalent to their estimated bodyweight.

The brain was removed and weighed, and the following tissues were taken and preserved in unspecified fixatives.

	CENTRAL NERVOUS SYSTEM
X	**BRAIN**
	Forebrain
	Center of cerebrum
	Midbrain
	Cerebellum
	Pons
	Medulla oblongata
	SPINAL CORD
X	Cervical swelling
X	Lumbar swelling
	OTHER
	Gasserian ganglion
	Trigeminal nerves
X	Optic nerve
X	Eyes

	PERIPHERAL NERVOUS SYSTEM
	SCIATIC NERVE
	Mid-thigh
X	Sciatic notch
	OTHER
	Sural nerve
X	Tibial nerve (proximal and distal)
	Peroneal nerve
X	Lumbar dorsal root fibers
X	Lumbar dorsal root ganglion
X	Lumbar ventral root fibers
X	Cervical dorsal root ganglion
X	Cervical dorsal root fibers
X	Cervical ventral root fibers
X	Gastrocnemius muscle

As the 0.40 mg/kg/day group was terminated prior to scheduled sacrifice, only tissues from the control, 0.12 and 0.20 mg/kg/day groups were processed. The brain was processed as on PND 12. The following tissues were trimmed, embedded in paraffin wax, sectioned, and stained with hematoxylin and eosin: transverse sections of the gastrocnemius muscle, eye with retina and optic nerve, spinal cord at cervical and lumbar swellings with the dorsal root ganglia and dorsal and ventral spinal root fibers; and longitudinal sections of the spinal cord at the cervical and lumbar swellings. The following tissues were embedded in resin and semi-thin sections cut and stained with toluidine blue: transverse and longitudinal sections of the proximal sciatic nerve, proximal tibial nerve, and distal tibial nerve (tibial nerve calf muscle branches). All processed tissues were examined microscopically.

Brain morphometric analysis was done for all surviving animals terminated at 12 and 63 days of age.

D. DATA ANALYSIS

1. **Statistical analyses:** Data were analyzed using SAS. The data were tested ($p \leq 0.05$ and ≤ 0.01) using the following statistical methods:

Parameter	Statistical Methods
Gestation body weights	Analysis of covariance (ANCOVA) on GD 7 body weight
Post partum body weights	ANCOVA on LD 1
Post partum body weights (LD 1); gestation food consumption during dosing and *post partum*; gestation length, litter size, initial (PND 1) mean pup body weight, and total litter weights; PND 5 litter-based mean body weights for F1 animals; motor activity measurements, the maximum amplitude and time to maximum amplitude in the startle response tests, the litter based mean time to preputial separation or vaginal opening, and mean litter bodyweights at the time of developmental landmarks, swimming times	Analysis of variance (ANOVA)
Pup body weights after PND 1	ANCOVA on PND 1, sexes separate
Proportion of litters with gestation length <22, 22, and >22 days	Fisher's Exact Test
Live born pups, pre-cull pup survival, pup sex, and percentage of successful trials in the Y-maze	Percentages were considered by ANOVA following double arcsine transformation of Freeman and Tukey.
Mean body weight in F1 animals after PND 5	ANCOVA on PND 5 bodyweights

Assuming that the assumptions of parametric analyses were verified prior to parametric analyses, the statistical analyses were considered appropriate.

2. **Indices**

a. **Reproductive indices:** The percentage of dams with gestation lengths of 22 days and >22 days was reported.

b. **Offspring viability indices:** The percentage of pups born live (live birth index), pups surviving at PND 5, whole litter losses, and male pups at PND 1 and 5 were reported. Additionally, the proportion of litters with all pups surviving until PND 5 was also reported. The reviewers calculated the viability index as the mean litter size on PND 5 x 100/ mean litter size on PND 1.

3. **Positive control data:** Positive control data were not provided with the current study. However, the reviewers have previously evaluated neurotoxicity studies from the performing lab that contained positive control data that validate the ability of the procedures and observers of the performing lab to detect the effect of chemicals on FOB parameters, motor activity, behavior, neuropathological lesions, and other parameters indicative of neurotoxicity. These data are summarized below.

Positive control data were obtained from MRIDs 45811002 (June 2000), 45811003 (June 2000), 46012923 (December 2001), 46336202 (November 2002), and 46336203 (June 2003). **Chlorpromazine HCl** (10 mg/kg bw; single i.p. dose; MRID 45811002) induced the following in both sexes: decreased activity; increased landing foot splay, and decreased forelimb grip strength. Additionally, the following differences from controls were noted: increased incidences of ptosis and urinary incontinence in females, increased time to tail flick in females, and decreased hindlimb grip strength in males. **Amphetamine sulfate** (10 mg/kg bw; single i.p. dose; MRID 45811002) induced the following in both sexes: increased activity, piloerection, salivation, and urinary incontinence; and decreased forelimb grip strength. Decreased hindlimb grip strength was also observed in males. **Morphine sulphate** (100 mg/kg bw; single gavage dose; MRID 45811003) induced increased time to tail flick in both sexes and decreased forelimb grip strength in females. **Buprenorphine** (300 mg/kg bw; single gavage dose; MRID 46012923) induced increased time to tail flick in both sexes. **Chlordiazepoxide** (20 mg/kg bw; single IP injection; MRID 46336202) induced decreased fore-limb grip strength in both sexes and decreased hind-limb grip strength in females. **Trimethyltin chloride** (6 or 8 mg/kg bw; IP injections on Days 1 and 7; MRID 46336203) induced in both sexes: (i) decreased overall motor activity; (ii) decreased response to sound; (iii) decreased width of the hippocampal dentate gyrus at level 4 (4HB); (iv) increased ataxia, clonic convulsions, tremors, and other clinical signs of neurotoxicity; (v) increased aggression; (vi) increased time to tail flick; and (vii) increased neuronal degeneration/necrosis in the hippocampus and piriform lobe of the brain. Additionally, decreased body weights were observed in males.

II. RESULTS

A. MATERNAL ANIMALS

1. **Mortality, clinical signs, and functional observations:** No treatment-related effects were observed on mortality, clinical signs, or functional observations. Three control dams (Nos. 17, 18, and 20) were sacrificed on LD 2 due to clinical signs (piloerection, hunched posture, pinched in sides, facial staining, vaginal bleeding, and signs of diarrhea). These animals had littered on GD 23. One 0.12 mg/kg/day female was found dead on LD 24. There were no changes in clinical condition observed prior to death and no evidence of a treatment-related effect. One 0.12 mg/kg/day female and two 0.40 mg/kg/day females were sacrificed on GD 25 because they had failed to litter. All three animals were found not to have been pregnant.

2. **Body weight and food consumption:** Selected group mean body weights and food consumption values for pregnant and nursing dams are presented in Table 2.

   Treatment-related increases ($p \leq 0.05$) in body weight were observed in the 0.20 and 0.40 mg/kg/day P females. These increases were observed during gestation beginning on GD 8 at both 0.20 mg/kg/day (↑1-4%) and 0.40 mg/kg/day (↑2-5%). Transient increases ($p \leq 0.05$) in body weight were also observed at 0.12 mg/kg/day from GD 9-15 (↑2%) and GD 19-22 (↑2-4%). Increased ($p \leq 0.01$) body weights were observed at 0.20 and 0.40 mg/kg/day on

LD 1 (↑5-6%), but thereafter body weights were similar to controls at all doses. Increases in body weight gain (calculated by reviewers) were observed on GD 7-22 and 1-22 (↑10-18%) in all treated groups. Concurrent increases ($p \leq 0.05$) in food consumption were observed on GD 7-15 and 15-22 (↑8-12%). Although treatment-related, these minor increases in body weight and food consumption were not considered adverse.

Decreases ($p \leq 0.05$) in food consumption were noted in the 0.40 mg/kg/day group during LD 5-8, 8-12, 12-15, 15-18, 18-21, and 21-23 (↓12-42%). However, body weights were similar to controls at this dose throughout lactation, and body weight gains (calculated by reviewers) were increased by 44% compared to controls from LD 1-29.

TABLE 2. Mean (±SD) maternal body weight and food consumption in rats exposed to Abamectin once daily via gavage from GD 7 through LD 22 [a]

Observations/study day	Dose (mg/kg/day) 0	0.12	0.20	0.40
Gestation (n=28-30)				
Body weight (g) GD 1	267.0±17.9	262.9±18.0	264.7±18.2	267.5±19.5
GD 7	301.9±26.3	299.8±17.7	298.5±15.9	303.6±19.0
GD 8	302.1	304.9	305.4* (↑1)	306.7** (↑2)
GD 9	305.3	309.9** (↑2)	310.6** (↑2)	311.6** (↑2)
GD 16	350.4	355.7	361.3** (↑3)	363.8** (↑4)
GD 22	426.4	441.5** (↑4)	445.1** (↑4)	448.8** (↑5)
Body weight gain (g) [b] GD 7-22	126.0	140.3 (↑11)	143.9 (↑14)	148.5 (↑18)
GD 1-22	160.9	177.2 (↑10)	177.7 (↑10)	184.6 (↑15)
Food consumption (g/animal/day) GD 7-15	20.4±2.3	22.1±2.4* (↑8)	22.6±2.9** (↑11)	22.7±2.9** (↑11)
GD 15-22	21.1±2.6	22.8±2.7* (↑8)	23.3±2.7** (↑10)	23.7±2.8** (↑12)
Lactation (n=18-24)				
Body weight (g) LD 1	336.5±24.9	344.7±19.1	353.7±20.3** (↑5)	357.0±25.3** (↑6)
LD 2	343.6	347.5	349.2	348.2
LD 29	358.2	356.1	355.5	366.8
Body weight gain (g) [b] LD 1-29	11.4	9.3	8.4	16.4 (↑44)
Food consumption (g/animal/day) LD 1-5	22.9±4.2	23.3±5.1	24.8±5.2	22.5±4.8
LD 5-8	35.1±6.5	35.7±4.7	36.0±4.3	30.8±6.3* (↓12)
LD 15-18	53.6±5.4	51.8±6.2	53.5±3.7	30.9±11.5** (↓42)
LD 21-23	63.8±7.8	63.8±4.7	66.5±5.5	54.6±9.6** (↓14)

a Data were obtained Table 5 on pages 63-65 of the study report. In the 0.4 mg/kg/day females, n=8-14 during LD 17-29. Except for GD 1 and GD 7, statistical analysis was performed on the adjusted means (ANCOVA analysis on GD 7). Percent difference from control (calculated by reviewers) is presented parenthetically.

b Calculated by reviewers from the unadjusted mean data in Table 5 on pages 63-65 of the study report.

* Statistically different from control, $p \leq 0.05$

** Statistically different from control, $p \leq 0.01$

3. **Reproductive performance:** No treatment-related effect on reproductive performance or gestation length was observed (Table 3).

TABLE 3. Reproductive performance [a]

Observation	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
Number mated	30	30	30	30
Number of litters	30	29	30	28
Intercurrent deaths	3	2	0	2
Mean (∀SD) gestation duration (days)	22.0±0.0	22.0±0.2	22.0±0.2	22.1±0.3
Incidence of dystocia	0	0	0	0

a Data were obtained from page 25 and Table 9 on page 72 of the study report.

4. **Maternal postmortem results:** Dams were not examined grossly or histologically except to verify pregnancy state.

B. **OFFSPRING:** Maternal treatment with 0.40 mg/kg/day was associated with high pup mortality (59/190 i.e. 31%) during pre-weaning; therefore, all dams and pups from this group were removed from the study. Due to the reduced number of litters/pups available for investigation and the severity of toxicity beginning on PND 8, the data from the 0.40 mg/kg/day group were excluded from statistical evaluation. The data, other than clinical observations and body weight, were not presented in the intergroup tables. However, it was stated that the individual data were included in the relevant appendices.

1. **Viability and clinical signs:** No treatment-related effects were observed on litter parameters (number born live, number born dead, sex ratio (% male), mean litter size, live birth index, and viability index; Table 4a) or clinical signs (including FOB) in the offspring from PND 1 through 5.

TABLE 4a. Litter size and viability [a]

Observation	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
Total number born	371	356	361	344
Number born live	369	356	358	342
Number born dead	2	0	3	2
Sex ratio Day 1 (% %)	52.7±17.5	51.2±18.4	48.2±16.3	51.3±16.1
# Deaths Days 1-5 (%)[b]	16	11	15	14
Mean litter size:				
Day 1	12.3±3.6	12.3±3.6	11.9±3.4	12.2±3.6
Day 5 (pre-cull)	11.4±3.4	11.9±3.5	11.5±3.2	11.8±3.3
Live birth index (%)	99.5	100	98.8	99.5
Viability index [c]	92.7	96.7	96.6	96.7

a Data obtained from Tables 10, 11, 14, & 15 on pages 73, 74, 77, & 78 of the study report.
b Found dead and missing
c Calculated by the reviewers from data in this table as the mean litter size on PND 5 x 100/ mean litter size on PND 1

Following culling on PND 5, mortality and associated clinical signs of toxicity were observed in the 0.40 mg/kg/day pups (Table 4b). A total of 32 males and 27 females were missing and presumed dead, found dead, or killed for humane reasons or due to clinical signs of toxicity. The pups were generally small in size and presented with dehydration (133-151 observations in 42-45 pups) and tremors (276-292 observations in 66-67 pups). Since these deaths left an insufficient number of pups to complete all of the study objectives, all dams and pups at this dose were removed from the study during PND 15-38.

TABLE 4b. Viability and clinical signs from PND 5 to termination [a]

Observation	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
Males				
Total mortality	2	2	2	32
Missing, presumed dead	0	1	1	7
Found dead	2	0	1	6
Killed for humane reasons	0	1	0	9
Killed due to clinical signs	0	0	0	10
Dehydrated (observations/animals)	0	0	0	133/45
Tremors (observations/animals)	0	0	0	276/66
Females				
Total mortality	2	2	0	27
Missing, presumed dead	2	2	0	4
Found dead	0	0	0	1
Killed for humane reasons	0	0	0	12
Killed due to clinical signs	0	0	0	10
Dehydrated (observations/animals)	0	0	0	151/42
Tremors (observations/animals)	0	0	0	292/67

a Data obtained from Table 18 on pages 81-86 of the study report.

2. **Body weight:** Offspring pre-weaning body weights were decreased ($p \leq 0.01$) by 10-36% compared to controls in the 0.40 mg/kg/day males and females from PND 8 (Table 5). There were no effects of treatment on the 0.12 or 0.2 mg/kg/day groups. The minor increase ($p \leq 0.05$) in offspring body weight noted in the 0.20 mg/kg/day males (↑9%) after culling on PND 5 was unrelated to dose.

TABLE 5. Mean (±SD) pre-weaning pup body weights (g) [a]

PND	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
	Males			
1	6.1±0.6	6.2±0.6	6.3±0.4	6.3±0.6
5[b]	9.8±1.5	9.8±1.4	10.3±1.2	9.6±1.2
5[c]	9.3±0.9	9.5±0.7	10.1±0.8* (↑9)	9.6±1.0
8	14.8±1.3	15.1±1.3	15.9±1.3	13.1±2.4** (↓11)
12	23.6±1.7	23.9±2.0	24.9±2.1	17.9±4.8** (↓24)
15	31.4±2.0	31.8±2.5	32.9±2.3	21.9±7.4** (↓30)
22	52.4±3.3	52.9±3.3	54.1±2.7	35.9±9.7** (↓31)
29	90.9±4.4	87.1±5.1	87.3±4.8	61.5±14.1** (↓32)
	Females			
1	5.8±0.5	5.8±0.5	5.9±0.5	6.0±0.7
5[b]	9.5±1.4	9.2±1.0	9.8±1.3	9.3±1.3
5[c]	9.0±0.8	9.2±0.8	9.6±0.8	9.4±1.1
8	14.3±1.1	14.8±1.4	15.2±1.2	12.9±2.4* (↓10)
12	23.1±1.4	23.5±2.3	24.1±2.0	17.2±5.1** (↓26)
15	30.9±2.7	31.3±2.7	32.1±2.4	21.9±7.9** (↓29)
22	51.2±3.6	51.5±3.3	52.5±2.8	33.5±10.9** (↓35)
29	86.7±4.5	81.6±4.4	82.0±4.6	55.8±16.0** (↓36)

a Data were obtained from Tables 16 and 20 on pages 79 and 123-126 of the study report. Percent differences from control (calculated by reviewers) are presented in parentheses. Statistical analyses (ANOVA followed by Dunnett's test, using the litter as the statistical unit) were performed by the reviewers on individual data obtained from Appendix 17 on pages 785-787, 791-793, 797-799, and 803-805, and Appendix 19 on pages 1790-1819 of the study report.

b Pre-cull; n=27-30

c Post-cull; n=8-24

* Significantly different from control, $p \leq 0.05$

** Significantly different from control, $p \leq 0.01$

Offspring post-weaning body weights were decreased ($p \leq 0.05$) by 30-33% in the 0.40 mg/kg/day males and females on PND 36 (Table 6). There were no surviving pups at this dose level after PND 38. Additionally, decreases ($p \leq 0.05$) in post-weaning body weight were observed in the 0.12 and 0.20 mg/kg/day groups (↓4-8%) throughout the post-weaning interval (PND 36-63).

The individual pup body weight data were re-evaluated using Mixed Model Analysis of Body Weight Data from Developmental Neurotoxicity Study by the statisticians of Chemistry and Exposure Branch. This analytical method takes into accounts of animals in the same litter and correlation of measures of the same animal. In addition, it analyzes the daily rate of body weight changes. Table 6a summarizes the comparative results of the pup body weight data (PND 36 to 63) for mid- and low dose groups. The results indicated that there was a statistically significant difference for mid- and low-dose males from the corresponding controls, and for females no statistical significant difference existed. However, the decrease in low-dose males was approximately 3% relative to the controls, and it was determined not to be toxicologically significant.

TABLE 6. Mean (±SD) post-weaning pup body weights (g) [a]				
PND	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
	Males			
36	142.0±82	136.3±8.2	134.2±8.2* (↓5)	99.8±18.7** (↓30)
43	196.4±8.6	189.6±11.3	186.1±11.3** (↓5)	—
50	255.7±11.5	245.6±14.1* (↓4)	242.0±14.4** (↓5)	—
57	313.0±13.7	299.5±18.7* (↓4)	293.2±17.4** (↓6)	—
63	353.2±12.8	334.7±21.6** (↓5)	328.4±19.1** (↓7)	—
	Females			
36	125.7±6.2	116.8±6.7** (↓7)	116.2±6.4** (↓8)	83.8±18.3** (↓33)
43	156.2±7.3	146.5±9.1** (↓6)	147.1±10.5** (↓6)	—
50	182.5±9.7	174.9±10.0* (↓4)	175.3±10.9* (↓4)	—
57	206.6±11.6	196.9±10.8* (↓4)	194.9±10.9** (↓6)	—
63	217.9±12.6	205.8±12.7** (↓6)	203.9±10.8** (↓6)	—

a Data were obtained from Table 20 on pages 123-126 of the study report; n=20-23, except for the 0.40 mg/kg/day group where n=8 on PND 29 and 36. Percent differences from control (calculated by reviewers) are presented in parentheses. Statistical analyses (ANOVA followed by Dunnett's test, using the litter as the statistical unit) were performed by reviewers on individual data obtained from Appendix 17 on pages 785-787, 791-793, 797-799, and 803-805, and Appendix 19 on pages 1790-1819 of the study report.

— No surviving pups

* Significantly different from control, p≤0.05

** Significantly different from control, p≤0.01

Table 6a. Summary of Mixed Model Analysis Results of the Pup Body Weight Data

Comparaison	Males			Feamles		
	Difference	% decrease	Adjusted P-value	Difference	% decrease	Adjusted P-value
Control-Low	12	3.3%	0.0021	7.0	3.2%	0.1413
Control-Mid	22	6.0%	<0.0001	9.2	4.3%	0.0529

3. Developmental landmarks

a. Sexual maturation: The age when vaginal opening occurred increased (p≤0.05) at 0.12 and 0.20 mg/kg/day (both 33.3 days) compared to controls (32.0 days; Table 7). Although the body weights at landmark were similar to controls in Table 7, examination of the body weight data in Table 6 revealed a 7-8% decrease (p≤0.01) in body weights at approximately the time of vaginal opening (PND 36). Therefore, the delay in vaginal opening was considered to be a result of delayed development associated with decreased growth. No effect of treatment was observed on the time to preputial separation.

TABLE 7. Mean (±SD) age of sexual maturation (days) [a]				
Parameter	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
N (M/F)	73/65	75/76	80/79	NP
N (# of litters)	20	22	23	NP
Preputial separation (males)	44.0±1.1	44.3±1.2	44.6±1.4	NP
Vaginal opening (females)	32.0±1.9	33.3±1.8*	33.3±1.9*	NP
BW in males at landmark (g)	207.3±9.7	200.8±10.9	201.3±14.5	NP
BW in females at landmark (g)	102.0±13.2	102.7±12.2	101.7±9.1	NP

a Data were obtained from Table 21 on pages 127-128 of the study report
NP Data not provided
* Significantly different from control, $p \leq 0.05$

b. Physical landmarks: Evaluation of physical landmarks was not performed.

4. Behavioral assessments

a. Functional observational battery: No treatment-related effects were observed during the functional observational battery at any dose on PND 5 or in the 0.12 and 0.20 mg/kg/day animals on PND 12, 22, 36, 46, or 61. Data were not provided for the 0.40 mg/kg/day animals after PND 5.

b. Motor activity: Motor activity data are presented in Tables 8a, b, and c. No treatment-related effect was observed on total motor activity. Habituation was unaffected by treatment. Motor activity at PNDs 18, 22, and 60 was generally greater than motor activity at PND 14. Differences ($p \leq 0.05$) from controls were sporadic and unrelated to treatment. Individual motor activity was provided on pages 129-136 of the study report and is included as an Appendix to this DER.

TABLE 8a. Mean (±S.D.) motor activity data (total activity counts for session) [a]				
Test Day	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
Males (n=10-12)				
PND 14	222.2±107.8 [49%]	201.1±118.0	205.8±155.0	NP
PND 18	285.3±154.4 [54%]	351.7±276.7	275.0±180.7	NP
PND 22	484.4±148.5 [31%]	372.4±185.7	487.3±206.6	NP
PND 60	592.7±133.7 [23%]	501.3±139.1	530.0±129.7	NP
Females (n=9-11)				
PND 14	155.9±145.7 [93%]	161.4±101.9	148.2±107.9	NP
PND 18	245.9±147.6 [60%]	281.5±162.8	279.0±185.4	NP
PND 22	380.4±158.9 [42%]	487.4±170.4	506.8±203.5	NP
PND 60	578.9±125.6 [22%]	556.9±109.8	545.9±130.0	NP

a Data were obtained from Tables 22-25 on pages 129-136 of the study report. Coefficients of variation (calculated by reviewers) are presented in brackets.
NP Data not provided

TABLE 8b. Mean (±S.D.) sub-session motor activity data in males (# movements/5 minute sub-session) [a]				
Interval (minutes)	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
PND 14				
1-5	44.7±23.7	55.4±31.2	38.0±33.1	NP
6-10	24.9±28.4	30.0±23.7	21.1±26.7	NP
11-15	24.3±33.8	19.7±23.6	30.3±26.1	NP
16-20	22.3±24.6	17.2±27.1	29.3±29.3	NP
21-25	24.8±24.2	17.5±21.2	27.4±37.6	NP
26-30	19.9±16.2	5.1±5.9	14.4±27.1	NP
31-35	15.8±29.0	10.1±16.4	20.7±27.7	NP
36-40	17.8±22.1	13.0±24.9	15.4±24.5	NP
41-45	15.4±27.7	17.9±28.3	4.9±10.1	NP
46-50	12.3±17.2	15.3±22.1	4.4±7.1	NP
PND 22				
1-5	50.8±27.6	38.2±32.2	45.5±30.2	NP
6-10	44.0±29.8	45.8±32.1	46.5±33.4	NP
11-15	33.0±30.0	36.0±34.3	33.2±32.0	NP
16-20	32.6±34.8	35.3±35.9	22.3±27.4	NP
21-25	23.4±24.7	35.2±37.2	31.2±33.2	NP
26-30	20.9±32.0	32.1±35.4	19.9±26.8	NP
31-35	18.2±21.9	30.3±33.0	21.6±27.2	NP
36-40	18.1±29.6	30.3±31.2	20.2±25.5	NP
41-45	18.6±29.0	39.3±38.7	21.5±28.2	NP
46-50	25.7±30.3	29.4±30.7	13.3±22.7	NP
PND 22				
1-5	67.3±12.9	59.8±25.0	60.0±28.1	NP
6-10	65.2±16.5	52.5±17.2	66.9±23.1	NP
11-15	41.3±27.4	41.0±34.0	38.6±22.8	NP
16-20	44.2±27.0	33.7±26.8	28.3±31.9	NP
21-25	42.6±28.8	34.0±27.4	44.1±37.6	NP
26-30	41.3±27.9	30.1±31.1	43.2±28.5	NP
31-35	51.4±35.2	33.6±31.0	44.1±33.3	NP
36-40	52.7±30.2	24.5±29.3* (↓54)	64.9±32.0	NP
41-45	43.4±28.6	32.0±25.7	49.5±25.4	NP
46-50	35.0±32.4	31.1±25.7	47.7±29.4	NP
PND 60				
1-5	74.9±8.2	66.0±10.3* (↓12)	71.9±8.6	NP
6-10	70.7±9.8	65.3±14.5	67.8±9.8	NP
11-15	69.4±9.7	66.4±14.7	76.3±14.1	NP
16-20	67.3±11.2	62.7±14.0	69.0±19.5	NP
21-25	61.7±21.3	55.8±27.2	62.8±17.7	NP
26-30	50.0±26.4	51.5±26.3	52.1±21.5	NP
31-35	49.8±35.0	41.5±28.4	36.9±25.6	NP
36-40	55.1±19.5	32.7±29.2	36.8±32.9	NP
41-45	50.6±27.7	32.0±30.3	24.3±24.5* (↓52)	NP
46-50	43.2±33.9	27.4±36.2	32.2±29.1	NP

a Data were obtained from Tables 22-25 on pages 129-136 of the study report. Percent differences from controls (calculated by reviewers) are presented in parentheses.

NP Data not provided

* Significantly different from control, $p \leq 0.05$

TABLE 8c. Mean (±S.D.) sub-session motor activity data in females (# movements/5 minute sub-session) [a]				
Interval (minutes)	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
PND 14				
1-5	21.6±13.1	29.5±23.0	45.4±25.5* (↑110)	NP
6-10	17.7±22.4	25.5±25.7	25.5±26.1	NP
11-15	12.9±25.7	33.0±26.5* (↑156)	3.5±3.2	NP
16-20	21.2±22.4	7.9±15.0	13.3±29.6	NP
21-25	22.8±20.9	5.5±6.6	19.4±28.6	NP
26-30	13.8±23.3	9.7±14.1	13.5±22.9	NP
31-35	9.6±16.4	12.2±17.8	8.1±13.7	NP
36-40	8.6±17.7	13.8±21.4	6.1±12.1	NP
41-45	14.7±25.9	14.5±21.4	9.7±12.3	NP
46-50	13.2±24.5	9.8±14.9	3.8±3.7	NP
PND 22				
1-5	22.9±14.7	52.8±23.2* (↑131)	54.3±30.3** (↑137)	NP
6-10	25.3±19.4	41.3±20.7	47.5±29.0* (↑88)	NP
11-15	17.9±22.5	31.6±28.2	25.7±24.8	NP
16-20	26.6±20.1	27.4±27.5	16.5±28.3	NP
21-25	32.1±29.8	20.6±25.0	19.9±29.0	NP
26-30	29.2±26.1	27.0±24.0	17.1±29.4	NP
31-35	29.6±28.2	28.6±32.2	27.7±23.5	NP
36-40	24.1±24.0	18.7±23.2	28.2±26.7	NP
41-45	20.9±29.7	12.8±25.2	22.5±21.0	NP
46-50	17.3±26.3	20.7±25.8	19.5±24.3	NP
PND 22				
1-5	60.8±13.5	70.5±15.5	73.4±20.3	NP
6-10	52.6±19.8	55.9±22.5	66.3±22.5	NP
11-15	43.2±27.3	47.0±28.2	49.3±27.5	NP
16-20	43.0±34.0	52.6±27.2	48.6±32.1	NP
21-25	35.1±25.4	44.7±32.7	47.6±25.0	NP
26-30	26.3±23.2	51.5±25.6* (↑96)	48.3±28.2	NP
31-35	20.1±26.6	45.3±27.7* (↑125)	54.7±23.6** (↑172)	NP
36-40	26.1±26.4	48.9±28.1	40.0±23.7	NP
41-45	37.7±28.7	43.9±30.2	40.8±23.7	NP
46-50	35.6±35.7	27.1±26.4	37.8±29.7	NP
PND 60				
1-5	66.8±12.1	60.6±11.4	59.3±10.6	NP
6-10	65.0±9.0	66.1±9.9	59.8±14.4	NP
11-15	60.1±7.9	62.6±7.6	60.2±10.7	NP
16-20	61.7±11.2	63.9±18.4	58.5±19.3	NP
21-25	65.2±12.8	55.4±24.4	49.8±21.8	NP
26-30	51.2±14.8	48.2±20.5	45.5±23.6	NP
31-35	48.6±20.6	49.9±19.4	46.5±19.7	NP
36-40	54.4±25.1	45.6±25.4	54.7±23.1	NP
41-45	52.6±22.0	44.9±23.5	56.3±26.5	NP
46-50	53.3±25.1	59.7±16.9	55.4±29.3	NP

a Data were obtained from Tables 22-25 on pages 129-136 of the study report. Percent differences from controls (calculated by reviewers) are presented in parentheses.

NP Data not provided

* Significantly different from control, $p \leq 0.05$

** Significantly different from control, $p \leq 0.01$

c. **Auditory startle reflex habituation:** No treatment-related effect was observed on the auditory startle reflex (Tables 9a and 9b). At PND 61, peak amplitude was decreased ($p \leq 0.05$) by 28% in the 0.12 and 0.20 mg/kg/day males during Block 4 and increased ($p \leq 0.01$) by 67% in the 0.20 mg/kg/day females during Block 1; however, these isolated differences were considered incidental.

Data for overall mean (±SD) acoustic startle peak amplitude and latency to peak were not provided in the summary tables of the report.

TABLE 9a. Mean (±SD) interval acoustic startle peak amplitude (g) and latency to peak (ms) in F1 male rats [a]

Dose (mg/kg/day)	Parameter	Block 1	Block 2	Block 3	Block 4	Block 5
PND 23						
0	Peak Amp.	471.4±188.5	318.4±115.3	262.7±73.2	222.6±59.7	201.2±63.3
	Latency	29.6±8.1	23.5±6.3	22.0±2.9	21.0±2.2	21.1±3.2
0.12	Peak Amp.	394.7±140.9	258.3±76.9	250.0±78.7	224.9±64.4	209.8±66.6
	Latency	24.6±3.9	23.1±4.3	20.3±2.4	20.2±2.4	19.7±1.4
0.20	Peak Amp.	411.8±176.7	256.1±76.1	227.8±72.8	222.0±76.0	205.5±59.3
	Latency	29.2±6.3	20.8±3.4	22.0±3.1	19.9±1.8	21.0±2.3
0.40	Peak Amp.	NP	NP	NP	NP	NP
	Latency	NP	NP	NP	NP	NP
PND 61						
0	Peak Amp.	1696.4±638.9	1063.0±522.7	1032.0±386.6	979.1±421.8	866.2±394.7
	Latency	29.5±5.7	23.7±5.3	22.1±3.3	24.5±3.9	23.6±3.2
0.12	Peak Amp.	1270.4±389.0	946.9±370.2	800.0±289.3	702.2±245.7*(↓28)	679.1±225.1
	Latency	24.3±3.3	21.6±2.5	21.5±2.8	22.2±3.0	22.9±2.5
0.20	Peak Amp.	1302.2±542.5	804.7±330.8	824.8±250.3	700.2±228.7*(↓28)	785.4±418.2
	Latency	26.4±8.2	22.5±2.6	22.7±2.9	23.5±2.7	22.1±2.8
0.40	Peak Amp.	NP	NP	NP	NP	NP
	Latency	NP	NP	NP	NP	NP

a Data were obtained from Tables 26-27 on pages 137, 139, 141, and 143 of the study report; n=10-12 with 10 trials/block. Percent difference from controls (calculated by reviewers) is presented parenthetically.

NP Data not provided

* Significantly different from controls at $p \leq 0.05$

TABLE 9b. Mean (±SD) interval acoustic startle peak amplitude (g) and latency to peak (ms) in F1 female rats [a]

Dose (mg/kg/day)	Parameter	Block 1	Block 2	Block 3	Block 4	Block 5
PND 23						
Control	Peak Amp.	334.0±104.1	294.9±118.1	264.8±103.3	240.2±62.6	213.6±49.9
	Latency	24.2±4.5	21.5±3.0	20.0±1.7	20.7±2.0	21.7±4.1
0.12	Peak Amp.	424.4±234.1	311.8±138.9	257.4±75.3	213.4±72.3	187.9±74.5
	Latency	26.2±6.9	21.4±5.1	20.8±2.4	21.4±2.6	20.8±2.1
0.20	Peak Amp.	558.9±276.5*(↑67)	375.8±134.3	343.9±120.1	263.9±47.3	229.3±55.5
	Latency	29.4±8.3	22.2±4.9	21.3±5.6	20.3±2.3	20.7±2.6
0.40	Peak Amp.	NP	NP	NP	NP	NP
	Latency	NP	NP	NP	NP	NP
PND 61						
Control	Peak Amp.	1039.0±223.5	819.5±185.9	830.9±236.0	689.1±203.5	630.0±208.0
	Latency	23.6±2.4	23.2±2.3	23.4±1.9	23.5±2.8	24.7±4.7
0.12	Peak Amp.	1008.0±227.6	771.0±192.1	728.4±182.2	732.1±162.6	690.4±185.0
	Latency	25.8±2.8	22.7±2.5	21.6±2.5	22.2±3.7	22.7±2.5
0.20	Peak Amp.	1184.0±640.9	954.4±477.2	824.9±329.3	712.6±281.4	618.8±264.5
	Latency	24.8±3.9	23.2±2.8	23.7±3.3	23.7±4.0	24.1±2.5
0.40	Peak Amp.	NP	NP	NP	NP	NP
	Latency	NP	NP	NP	NP	NP

a Data were obtained from Tables 26-27 on pages 138, 140, 142, and 144 of the study report; n=9-11 with 10 trials/block. Percent difference from controls (calculated by reviewers) is presented parenthetically.
NP Data not provided
* Significantly different from controls at $p \leq 0.05$

d. **Learning and memory testing:** No treatment-related differences in learning or memory were noted in any treated group relative to concurrent controls in the water maze tests on PND 24/27 or 59/62 (Tables 10a and 10b). Learning was demonstrated based on the decreased time to complete the maze on Trial 6 vs Trial 1 in the learning phase. Typically, less than half the time was required for maze completion on Trial 6 compared to Trial 1. Memory was demonstrated in that the first trial in the memory phase was completed in less time required for the first trial in the learning phase. The differences ($p \leq 0.05$) noted were sporadic, unrelated to dose, and/or improvements over the control. The proportion of successful trials was calculated as the number of trials completed in less than 3, 4, 5, 6, 7, 8, 9, or 10 seconds or less than 1.0x, 1.5x, or 2.0x the time required to complete the straight channel (Tables 11a and 11b). The differences ($p \leq 0.05$) in the proportion of successful trials were either increases in successes over the controls or were not dose-related.

TABLE 10a. Water maze performance: Mean (±SD) swimming time (sec) on PND 24 and 27 [a]

Session/Parameter		Dose (mg/kg/day)			
		0	0.12	0.20	0.40
Males					
Learning Phase, PND 24	Straight channel	7.12±6.28	5.48±4.40	4.50±3.56	NP
	Latency trial 1	16.23±7.95	14.54±7.45	12.81±7.89	NP
	Latency trial 2	10.27±6.92	9.94±7.06	9.57±7.59	NP
	Latency trial 3	7.62±5.24	10.23±6.53	8.80±6.37	NP
	Latency trial 4	5.11±2.96	7.70±5.84	7.95±6.24	NP
	Latency trial 5	7.45±4.81	5.18±2.08	7.40±5.41	NP
	Latency trial 6	7.44±4.75	5.47±3.59	6.60±7.03	NP
Memory Phase, PND 27	Straight channel	6.44±4.21	4.72±2.16	4.16±2.16*(↓35)	NP
	Latency trial 1	7.10±4.87	7.63±5.25	8.06±4.28	NP
	Latency trial 2	6.45±4.96	4.66±2.43	4.41±2.57	NP
	Latency trial 3	4.98±4.48	5.25±5.83	3.71±2.22	NP
	Latency trial 4	7.27±6.55	5.19±4.53	3.40±1.54**(↓53)	NP
	Latency trial 5	5.81±4.69	4.84±3.29	6.99±6.98	NP
	Latency trial 6	6.59±4.63	4.83±2.81	5.27±4.17	NP
Females					
Learning Phase, PND 24	Straight channel	5.95±3.97	5.62±3.50	4.81±3.40	NP
	Latency trial 1	18.81±8.28	15.30±6.61	18.84±6.96	NP
	Latency trial 2	7.21±4.28	8.90±4.73	9.56±6.94	NP
	Latency trial 3	6.04±4.36	8.51±6.46	6.28±4.54	NP
	Latency trial 4	7.72±4.59	7.29±5.18	8.51±5.57	NP
	Latency trial 5	5.99±4.94	5.96±3.09	6.16±5.64	NP
	Latency trial 6	5.93±5.36	6.15±4.66	7.56±6.19	NP
Memory Phase, PND 27	Straight channel	4.06±2.57	4.68±2.11	4.45±1.85	NP
	Latency trial 1	8.35±6.42	9.29±5.47	7.02±4.39	NP
	Latency trial 2	6.89±5.44	6.18±5.29	4.54±2.89	NP
	Latency trial 3	5.70±4.62	5.56±4.17	4.62±4.47	NP
	Latency trial 4	5.28±3.30	5.17±5.19	5.89±5.51	NP
	Latency trial 5	6.53±4.74	5.97±5.11	6.04±4.45	NP
	Latency trial 6	8.36±5.66	7.93±5.54	5.99±4.30	NP

a Data were obtained from Table 28 on pages 145-148 of the study report. Percent difference from controls (calculated by reviewers) is presented parenthetically.

NP Data not provided

* Statistically different from control, $p \leq 0.05$

TABLE 10b. Water maze performance: Mean (±SD) swimming time (sec) on PND 59 and 62 [a]

Session/Parameter		Dose (mg/kg/day)			
		0	0.12	0.20	0.40
Males					
Learning Phase, PND 59	Straight channel	4.48±2.00	4.23±1.64	4.98±2.89	NP
	Latency trial 1	9.08±3.05	8.60±2.68	11.49±4.55*(↑27)	NP
	Latency trial 2	5.67±3.81	5.59±4.06	4.98±2.05	NP
	Latency trial 3	4.45±1.86	3.79±2.19	4.66±2.56	NP
	Latency trial 4	4.10±2.53	4.12±2.11	4.04±2.00	NP
	Latency trial 5	4.83±2.98	3.65±2.09	4.18±3.44	NP
	Latency trial 6	4.51±2.55	5.51±5.60	3.60±2.38	NP
Memory Phase, PND 62	Straight channel	2.91±1.09	2.46±0.72	3.29±1.05	NP
	Latency trial 1	5.54±3.17	4.34±2.97	6.22±4.52	NP
	Latency trial 2	4.81±2.92	5.04±5.10	3.89±2.39	NP
	Latency trial 3	4.26±2.60	6.95±6.73	5.93±5.27	NP
	Latency trial 4	6.81±5.79	6.03±5.94	7.18±6.10	NP
	Latency trial 5	6.87±5.37	7.68±6.85	10.37±8.88	NP
	Latency trial 6	5.85±3.99	5.82±4.76	8.07±6.76	NP
Females					
Learning Phase, PND 59	Straight channel	4.29±1.35	3.89±1.82	4.65±2.88	NP
	Latency trial 1	10.97±4.26	14.83±6.30*(↑35)	9.21±2.96	NP
	Latency trial 2	7.66±5.34	6.96±4.09	6.04±4.43	NP
	Latency trial 3	6.61±4.55	5.78±6.02	5.80±4.99	NP
	Latency trial 4	4.48±2.64	4.16±2.75	6.71±7.53	NP
	Latency trial 5	4.84±2.27	3.92±2.16	4.97±3.28	NP
	Latency trial 6	5.18±3.50	5.33±3.29	4.69±3.40	NP
Memory Phase, PND 62	Straight channel	3.42±2.39	2.76±0.99	2.80±1.19	NP
	Latency trial 1	4.78±2.53	5.72±2.81	4.79±3.35	NP
	Latency trial 2	4.84±2.88	5.91±4.80	6.60±6.96	NP
	Latency trial 3	5.84±6.44	9.38±9.79	8.80±10.14	NP
	Latency trial 4	6.82±3.67	8.26±7.21	7.21±7.80	NP
	Latency trial 5	7.83±9.10	9.73±8.60	8.11±8.50	NP
	Latency trial 6	9.37±8.22	11.95±8.68	9.77±7.58	NP

a Data were obtained from Table 28 on pages 149-152 of the study report. Percent difference from controls (calculated by reviewers) is presented parenthetically.

NP Data not provided

* Statistically different from control, $p \leq 0.05$

TABLE 11a. Water maze performance: Mean (±SD) proportion of successful trials on PND 24 and 27 [a]

Session/Parameter		Dose (mg/kg/day) 0	0.12	0.20	0.40
Males					
Learning Phase, PND 24	Cut-off 3 sec	7.9±11.6	12.1±13.8	13.0±15.9	NP
	Cut-off 4 sec	32.5±18.8	30.3±22.8	26.8±22.3	NP
	Cut-off 5 sec	38.6±18.5	35.6±23.2	39.9±25.0	NP
	Cut-off 6 sec	43.0±21.7	45.5±21.3	47.1±25.0	NP
	Cut-off 7 sec	50.0±20.8	54.5±22.5	54.3±24.2	NP
	Cut-off 8 sec	55.3±22.9	59.1±20.4	58.7±23.0	NP
	Cut-off 9 sec	60.5±22.4	65.2±22.4	66.7±24.1	NP
	Cut-off 10 sec	66.7±21.5	70.5±22.4	71.7±25.3	NP
	Cut-off 1.0x straight channel	39.5±33.0	29.5±34.9	28.3±33.5	NP
	Cut-off 1.5x straight channel	56.1±31.0	50.0±32.1	47.8±36.7	NP
	Cut-off 2.0x straight channel	67.5±29.6	60.6±26.0	53.6±36.2	NP
Memory Phase, PND 27	Cut-off 3 sec	23.7±26.2	32.6±26.0	38.4±28.2	NP
	Cut-off 4 sec	44.7±26.7	50.0±26.2	56.5±32.5	NP
	Cut-off 5 sec	57.9±28.0	64.4±23.7	64.5±24.8	NP
	Cut-off 6 sec	64.9±27.7	75.0±24.0	73.2±21.8	NP
	Cut-off 7 sec	72.8±23.0	78.8±23.1	76.1±21.8	NP
	Cut-off 8 sec	76.3±23.1	85.6±23.2	81.2±18.3	NP
	Cut-off 9 sec	79.8±21.2	87.9±22.5	85.5±14.5	NP
	Cut-off 10 sec	83.3±20.8	90.9±15.2	88.4±13.7	NP
	Cut-off 1.0x straight channel	53.5±35.8	53.0±34.4	42.0±33.3	NP
	Cut-off 1.5x straight channel	70.2±31.7	72.0±31.9	71.7±24.3	NP
	Cut-off 2.0x straight channel	84.2±23.9	82.6±24.4	77.5±21.7	NP
Females					
Learning Phase, PND 24	Cut-off 3 sec	14.0±15.0	15.2±17.7	16.7±20.1	NP
	Cut-off 4 sec	31.6±21.4	25.8±21.7	34.1±23.3	NP
	Cut-off 5 sec	43.9±18.6	36.4±19.0	41.3±26.5	NP
	Cut-off 6 sec	50.9±17.1	43.9±20.9	47.1±22.8	NP
	Cut-off 7 sec	57.9±21.1	51.5±22.9	50.7±19.8	NP
	Cut-off 8 sec	63.2±21.2	54.5±23.1	54.3±18.3	NP
	Cut-off 9 sec	67.5±18.8	59.1±27.1	58.7±15.8	NP
	Cut-off 10 sec	71.9±20.1	69.7±21.6	62.3±15.3	NP
	Cut-off 1.0x straight channel	31.6±31.4	31.8±31.7	23.9±32.1	NP
	Cut-off 1.5x straight channel	55.3±27.8	53.8±30.0	45.7±29.4	NP
	Cut-off 2.0x straight channel	68.4±28.3	65.2±24.6	55.8±31.6	NP
Memory Phase, PND 27	Cut-off 3 sec	26.3±29.6	22.7±21.5	37.0±30.5	NP
	Cut-off 4 sec	41.2±26.9	46.2±23.0	55.1±24.8	NP
	Cut-off 5 sec	50.0±26.6	57.6±23.4	63.0±24.6	NP
	Cut-off 6 sec	56.1±23.7	63.6±20.3	68.8±20.3	NP
	Cut-off 7 sec	64.9±22.1	70.5±19.2	73.2±21.2	NP
	Cut-off 8 sec	70.2±22.6	73.5±19.0	75.4±21.8	NP
	Cut-off 9 sec	73.7±22.4	77.3±20.9	79.7±19.4	NP
	Cut-off 10 sec	73.7±22.4	80.3±18.3	83.3±17.4	NP
	Cut-off 1.0x straight channel	39.5±27.9	43.2±32.0	48.6±26.5	NP
	Cut-off 1.5x straight channel	57.0±29.6	62.1±26.8	73.2±22.9* (↑28)	NP
	Cut-off 2.0x straight channel	66.7±27.8	75.0±21.1	78.3±19.7	NP

a Data were obtained from Table 29 on pages 153-160 of the study report. Percent difference from controls (calculated by reviewers) is presented parenthetically.

NP Data not provided

* Statistically different from control, $p \leq 0.05$

TABLE 11b. Water maze performance: Mean (±SD) proportion of successful trials on PND 59 and 62 [a]

Session/Parameter		Dose (mg/kg/day) 0	0.12	0.20	0.40
Males					
Learning Phase, PND 59	Cut-off 3 sec	20.4±25.3	35.0±28.0	35.0±24.1	NP
	Cut-off 4 sec	47.2±27.6	54.2±24.1	54.2±21.5	NP
	Cut-off 5 sec	56.5±27.5	62.5±18.6	61.7±20.3	NP
	Cut-off 6 sec	65.7±20.2	72.5±20.4	70.8±14.2	NP
	Cut-off 7 sec	77.8±16.2	78.3±16.3	75.0±14.8	NP
	Cut-off 8 sec	82.4±16.6	83.3±10.8	78.3±10.9	NP
	Cut-off 9 sec	88.9±11.4	87.5±13.1	85.8±12.4	NP
	Cut-off 10 sec	91.7±11.8	90.0±12.6	86.7±12.8	NP
	Cut-off 1.0x straight channel	47.2±33.9	52.5±27.2	52.5±32.1	NP
	Cut-off 1.5x straight channel	71.3±24.8	74.2±19.1	72.5±23.1	NP
	Cut-off 2.0x straight channel	82.4±17.6	83.3±13.2	83.3±17.1	NP
Memory Phase, PND 62	Cut-off 3 sec	29.6±22.5	42.5±32.7	24.2±23.2	NP
	Cut-off 4 sec	47.2±27.0	55.0±30.2	49.2±27.3	NP
	Cut-off 5 sec	56.5±24.3	59.2±28.3	55.8±26.6	NP
	Cut-off 6 sec	65.7±22.5	70.8±22.2	64.2±25.5	NP
	Cut-off 7 sec	74.1±20.0	73.3±22.6	70.8±22.2	NP
	Cut-off 8 sec	79.6±17.7	75.0±22.6	73.3±21.2	NP
	Cut-off 9 sec	82.4±15.6	77.5±20.4	78.3±21.7	NP
	Cut-off 10 sec	87.0±14.6	79.2±19.4	79.2±22.2	NP
	Cut-off 1.0x straight channel	31.5±30.7	20.0±28.9	22.5±28.8	NP
	Cut-off 1.5x straight channel	49.1±35.5	52.5±31.7	48.3±25.3	NP
	Cut-off 2.0x straight channel	59.3±29.3	62.5±27.5	68.3±20.2	NP
Females					
Learning Phase, PND 59	Cut-off 3 sec	26.7±28.7	21.4±24.8	28.6±25.9	NP
	Cut-off 4 sec	40.0±35.5	46.0±26.3	44.4±24.3	NP
	Cut-off 5 sec	48.9±29.2	54.0±21.7	54.0±23.5	NP
	Cut-off 6 sec	58.9±29.5	65.1±15.7	65.1±21.0	NP
	Cut-off 7 sec	63.3±25.4	68.3±14.8	70.6±18.9	NP
	Cut-off 8 sec	65.6±24.0	72.2±15.2	77.0±15.3	NP
	Cut-off 9 sec	72.2±23.3	75.4±15.5	80.2±15.5	NP
	Cut-off 10 sec	78.9±21.3	79.4±12.8	83.3±13.9	NP
	Cut-off 1.0x straight channel	36.7±31.6	36.5±33.6	42.1±33.2	NP
	Cut-off 1.5x straight channel	55.6±30.0	58.7±25.6	58.7±34.4	NP
	Cut-off 2.0x straight channel	75.6±18.8	66.7±19.0	69.0±30.9	NP
Memory Phase, PND 62	Cut-off 3 sec	36.7±26.9	36.5±32.3	34.1±31.4	NP
	Cut-off 4 sec	46.7±29.7	44.4±34.3	48.4±31.6	NP
	Cut-off 5 sec	53.3±23.7	49.2±30.9	58.7±29.2	NP
	Cut-off 6 sec	61.1±17.4	54.0±30.7	65.9±28.1	NP
	Cut-off 7 sec	67.8±19.4	56.3±31.4	68.3±29.3	NP
	Cut-off 8 sec	75.6±17.7	62.7±31.6	72.2±29.5	NP
	Cut-off 9 sec	78.9±13.3	65.1±-31.6	75.4±28.7	NP
	Cut-off 10 sec	85.6±13.9	67.5±28.6* (↓21)	80.2±25.6	NP
	Cut-off 1.0x straight channel	25.6±30.1	23.8±31.4	21.4±28.9	NP
	Cut-off 1.5x straight channel	52.2±25.9	39.7±36.3	45.2±35.8	NP
	Cut-off 2.0x straight channel	61.1±24.9	54.0±32.9	61.1±32.2	NP

a Data were obtained from Table 29 on pages 161-168 of the study report. Percent difference from controls (calculated by reviewers) is presented parenthetically.

NP Data not provided

* Statistically different from control, $p \leq 0.05$

5. Postmortem results

a. Brain weights: No treatment-related effects were observed on brain weights of offspring on PND 12 or 63 (Table 12). A minor increase ($p \leq 0.05$) of 3% was noted in the brain weight of the 0.12 mg/kg/day females on PND 12.

TABLE 12. Mean (±SD) brain weight data [a]

Parameter	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
Males				
Day 12				
Brain weight (g)	1.11±0.03	1.09±0.07	1.10±0.05	NP
PND 63 (non-perfused)				
Brain weight (g)	2.00±0.05	1.99±0.05	1.98±0.03	NP
PND 63 (perfused)				
Brain weight (g)	2.11±0.11	2.07±0.10	2.08±0.10	NP
Females				
Day 12				
Brain weight (g)	1.04±0.04	1.07±0.03* (↑3)	1.06±0.03	NP
PND 63 (non-perfused)				
Brain weight (g)	1.86±0.05	1.86±0.06	1.85±0.06	NP
PND 63 (perfused)				
Brain weight (g)	1.93±0.04	1.93±0.07	1.88±0.09	NP

a Data were obtained from Tables 30-32 on pages 169-171 of the study report; n=10-12. Percent difference from controls (calculated by reviewers) is presented parenthetically.
NP Data not provided
* Statistically different from control, $p<0.05$

b. Neuropathology

1. Macroscopic examination: No treatment-related gross pathological findings were noted.

2. Microscopic examination: No treatment-related histopathological findings were observed in the 0.12 and 0.20 mg/kg/day groups at PND 12 or 63. Microscopic lesions (minimal nerve fiber degeneration/demyelination) in the proximal sciatic and proximal and distal tibial nerves were noted in the 0.12 and 0.20 mg/kg/day animals on PND 63. However, as these lesions were observed with equal or greater frequency in the controls and the severity was minimal, they were not considered to be related to treatment.

Morphometric evaluation of the brain revealed that no treatment-related effects were observed at 0.12 or 0.20 mg/kg/day in either sex on PND 12 or 63 (Tables 13a, 13b, 14a, and 14b). On PND 12, the following decreases ($p \leq 0.05$) were noted at 0.20 mg/kg/day: (i) level 4 dorsal cortex thickness in the males (↓6%); (ii) thickness of the inner granular layer of the preculminate fissure of the cerebellum in the males (↓11%); and (iii) thickness of the outer granular layer of the preculminate fissure of the cerebellum in the females (↓11%). These findings were considered incidental and unrelated to treatment as they were minor, generally within the range of historical controls (provided in Appendix 8 on pages 227 and

228 of the study report), and showed no consistent pattern in terms of location or sex distribution.

On PND 63, the overall width of the thalamus/cortex was decreased ($p \leq 0.05$) by 4% in the 0.20 mg/kg/day males compared to controls. However, as this decrease was minor and there were no other effects noted on the thalamus/cortex in either sex, this finding was considered incidental.

At 0.12 mg/kg/day, on both PND 12 and 63, the was a number of decreases ($p \leq 0.05$) from control noted in the brain measurements indicating a reduction in size. It was stated that investigations into the cause of these differences indicted that they may in part be attributable to the additional length of storage time of the brain in a wax block and, therefore, direct comparison with the control group is not appropriate. These investigations were reported in Appendix 6 on pages 223-224 of the study report.

TABLE 13a. Mean (±SD) morphometric data in F1 males on PND 12 [a]

Parameter	Level	Dose (mg/kg/day)			
		0	0.12	0.20	0.40
Frontal cortex - Height	2	5.69±0.12	4.96±0.19**(↓13)	5.59±0.19	NP
Frontal cortex - Width	2	4.72±0.14	4.02±0.11**(↓15)	4.61±0.17	NP
Dorsal cortex 1	3	1.19±0.03	1.04±0.08**(↓13)	1.20±0.07	NP
Dorsal cortex 2	3	1.29±0.11	1.12±0.07**(↓13)	1.32±0.05	NP
Piriform cortex	3	0.86±0.08	0.89±0.08	0.88±0.06	NP
Hippocampus – Length from midline	3	2.72±0.28	2.36±0.31**(↓13)	2.79±0.26	NP
Dorsal cortex	4	1.14±0.04	0.95±0.05**(↓17)	1.07±0.09*(↓6)	NP
Piriform cortex	4	0.90±0.04	0.87±0.06	0.86±0.11	NP
Corpus callosum	4	0.59±0.10	0.50±0.08	0.63±0.12	NP
Thalamus - Height	4	5.10±0.24	4.31±0.15**(↓15)	5.07±0.30	NP
Thalamus - Width	4	7.58±0.43	6.72±0.26**(↓11)	7.75±0.35	NP
Thalamus/cortex – Overall width	4	12.50±0.38	10.89±0.36**(↓13)	12.49±0.40	NP
Hippocampus – Length from midline	4	3.50±0.30	2.91±0.18**(↓17)	3.50±0.18	NP
Hippocampus – Width dentate gyrus	4	0.44±0.03	0.41±0.03**(↓7)	0.46±0.04	NP
Hippocampus – Length dentate gyrus	4	1.01±0.12	0.88±0.09**(↓13)	1.10±0.10	NP
Dorsal cortex	5	1.09±0.06	1.00±0.06**(↓8)	1.13±0.07	NP
Piriform cortex	5	0.98±0.08	0.95±0.06	0.96±0.10	NP
Thalamus - Width	5	6.84±0.45	5.97±0.27**(↓13)	6.77±0.31	NP
Hippocampus – Width dentate gyrus	5	0.53±0.05	0.55±0.04	0.55±0.04	NP
Hippocampus – Width overall	5	1.10±0.06	1.02±0.06**(↓7)	1.10±0.07	NP
Cerebellum – Height		3.56±0.09	3.36±0.13	3.70±0.27	NP
Cerebellum – Length		4.39±0.27	3.91±0.29*(↓11)	4.25±0.45	NP
Cerebellum – Preculminate fissure – Inner granular layer		114±11	82±11**(↓28)	101±9*(↓11)	NP
Cerebellum – Preculminate fissure – Molecular layer		74.5±5.3	69.3±9.6	77.7±8.4	NP
Cerebellum – Preculminate fissure – Outer granular layer		34.6±5.2	34.3±6.1	36.1±5.9	NP
Cerebellum – Prepyramidal fissure – Inner granular layer		99±24	75±11**(↓24)	94±11	NP
Cerebellum – Prepyramidal fissure – Molecular layer		59.2±11.6	56.8±5.3	60.6±6.6	NP
Cerebellum – Prepyramidal fissure – Outer granular layer		39.9+±6.5	36.8±2.9	38.8±5.2	NP

a Data were obtained from Table 33 on pages 172-176 of the study report; n=7-11. Percent difference from controls (calculated by reviewers) is presented parenthetically.

NP Data not provided

* Statistically different from control, $p \leq 0.05$

** Statistically different from control, $p \leq 0.01$

TABLE 13b. Mean (±SD) morphometric data in F1 females on PND 12 [a]

Parameter	Level	Dose (mg/kg/day)			
		0	0.12	0.20	0.40
Frontal cortex - Height	2	5.43±0.18	4.85±0.14**(↓11)	5.54±0.22	NP
Frontal cortex - Width	2	4.62±0.14	4.00±0.19**(↓13)	4.61±0.21	NP
Dorsal cortex 1	3	1.15±0.05	1.04±0.07**(↓10)	1.16±0.11	NP
Dorsal cortex 2	3	1.28±0.09	1.13±0.06**(↓12)	1.32±0.13	NP
Piriform cortex	3	0.83±0.09	0.92±0.07	0.82±0.12	NP
Hippocampus – Length from midline	3	2.76±0.15	2.23±0.17**(↓19)	2.75±0.21	NP
Dorsal cortex	4	1.10±0.07	0.97±0.07**(↓12)	1.10±0.10	NP
Piriform cortex	4	0.86±0.10	0.84±0.06	0.89±0.09	NP
Corpus callosum	4	0.67±0.06	0.50±0.05**(↓25)	0.66±0.11	NP
Thalamus - Height	4	5.06±0.23	4.30±0.17**(↓15)	5.17±0.23	NP
Thalamus - Width	4	7.63±0.42	6.62±0.27**(↓13)	7.73±0.42	NP
Thalamus/cortex – Overall width	4	12.11±0.48	10.89±0.33**(↓10)	12.32±0.36	NP
Hippocampus – Length from midline	4	3.43±0.18	2.93±0.18**(↓15)	3.46±0.25	NP
Hippocampus – With dentate gyrus	4	0.45±0.03	0.41±0.03*(↓9)	0.46±0.03	NP
Hippocampus – Length dentate gyrus	4	0.98±0.11	0.92±0.13	0.99±0.06	NP
Dorsal cortex	5	1.10±0.10	0.99±0.04**(↓10)	1.09±0.07	NP
Piriform cortex	5	0.92±0.10	0.95±0.04	0.98±0.12	NP
Thalamus - Width	5	6.70±0.38	5.85±0.29**(↓13)	6.82±0.44	NP
Hippocampus – With dentate gyrus	5	0.54±0.03	0.52±0.04	0.56±0.05	NP
Hippocampus – Width overall	5	1.12±0.10	0.98±0.06**(↓13)	1.11±0.07	NP
Cerebellum – Height		3.56±0.27		3.51±0.35	NP
Cerebellum – Length		4.17±0.33	3.48±0.11*(↓17)	4.05±0.34	NP
Cerebellum – Preculminate fissure – Inner granular layer		111±9	83±8**(↓25)	105±12	NP
Cerebellum – Preculminate fissure – Molecular layer		76.4±5.7	68.7±9.7*(↓10)	75.7±9.0	NP
Cerebellum – Preculminate fissure – Outer granular layer		38.3±2.1	33.9±7.2*(↓11)	34.0±3.8*(↓11)	NP
Cerebellum – Prepyramidal fissure – Inner granular layer		97±10	75±15**(↓23)	91±9	NP
Cerebellum – Prepyramidal fissure – Molecular layer		57.1±6.6	57.3±9.0	62.9±4.5	NP
Cerebellum – Prepyramidal fissure – Outer granular layer		38.7±6.8	40.6±7.2	41.8±4.2	NP

a Data were obtained from Table 33 on pages 177-181 of the study report; n=6-12. Percent difference from controls (calculated by reviewers) is presented parenthetically.

NP Data not provided

* Statistically different from control, p≤0.05

** Statistically different from control, p≤0.01

TABLE 14a. Mean (±SD) morphometric data in F1 males on PND 63 [a]

Parameter	Level	Dose (mg/kg/day)			
		0	0.12	0.20	0.40
Frontal cortex - Height	2	7.03±0.46	6.46±0.44**(↓8)	7.05±0.35	NP
Frontal cortex - Width	2	5.17±0.26	4.78±0.21**(↓8)	5.19±0.40	NP
Dorsal cortex 1	3	1.28±0.12	1.18±0.12	1.20±0.11	NP
Dorsal cortex 2	3	1.54±0.17	1.51±0.10	1.44±0.10	NP
Piriform cortex	3	1.11±0.10	1.08±0.07	1.07±0.05	NP
Hippocampus – Length from midline	3	2.76±0.24	2.40±0.19*(↓13)	2.71±0.41	NP
Dorsal cortex	4	1.22±0.13	1.05±0.10**(↓14)	1.19±0.10	NP
Piriform cortex	4	1.11±0.10	1.01±0.09*(↓9)	1.15±0.14	NP
Corpus callosum	4	0.40±0.04	0.36±0.06	0.38±0.06	NP
Thalamus - Height	4	5.25±0.25	4.72±0.25**(↓10)	5.21±0.28	NP
Thalamus - Width	4	8.41±0.34	7.84±0.35**(↓7)	8.26±0.43	NP
Thalamus/cortex – Overall width	4	14.38±0.62	13.07±0.44*(↓9)	13.75±0.68*(↓4)	NP
Hippocampus – Length from midline	4	3.30±0.23	3.28±0.24	3.24±0.28	NP
Hippocampus – With dentate gyrus	4	0.59±0.04	0.52±0.02**(↓12)	0.57±0.04	NP
Hippocampus – Length dentate gyrus	4	1.60±0.10	1.39±0.16**(↓13)	1.54±0.13	NP
Dorsal cortex	5	1.38±0.10	1.25±0.07**(↓9)	1.40±0.07	NP
Piriform cortex	5	1.14±0.08	1.05±0.06*(↓8)	1.18±0.09	NP
Thalamus - Width	5	7.78±0.30	7.11±0.30**(↓9)	7.84±0.40	NP
Hippocampus – With dentate gyrus	5	0.67±0.04	0.61±0.05**(↓9)	0.66±0.04	NP
Hippocampus – Width overall	5	1.45±0.05	1.30±0.07**(↓10)	1.47±0.09	
Cerebellum – Height		5.34±0.35	4.80±0.34**(↓10)	5.43±0.36	NP
Cerebellum – Length		6.85±0.41	6.15±0.35**(↓10)	6.73±0.31	NP
Cerebellum – Preculminate fissure – Inner granular layer		147±21	114±9**(↓22)	141±22	NP
Cerebellum – Preculminate fissure – Molecular layer		199.9±19.9	186.8±13.2	189.7±19.0	NP
Cerebellum – Prepyramidal fissure – Inner granular layer		136±26	97±22**(↓29)	144±21	NP
Cerebellum – Prepyramidal fissure – Molecular layer		193.2±22.7	169.4±18.4*(↓12)	192.8±22.7	NP

a Data were obtained from Table 34 on pages 182-186 of the study report; n=6-11. Percent difference from controls (calculated by reviewers) is presented parenthetically.

NP Data not provided

* Statistically different from control, $p \leq 0.05$

** Statistically different from control, $p \leq 0.01$

TABLE 14b. Mean (±SD) morphometric data in F1 females on PND 63 [a]

Parameter	Level	Dose (mg/kg/day)			
		0	0.12	0.20	0.40
Frontal cortex - Height	2	6.73±0.42	6.29±0.26*(↓7)	6.88±0.39	NP
Frontal cortex - Width	2	4.99±0.22	4.61±0.23**(↓8)	4.98±0.29	NP
Dorsal cortex 1	3	1.21±0.09	1.18±0.11	1.24±0.09	NP
Dorsal cortex 2	3	1.38±0.17	1.48±0.14	1.45±0.18	NP
Piriform cortex	3	1.08±0.09	1.07±0.11	1.07±0.12	NP
Hippocampus – Length from midline	3	2.42±0.29	2.36±0.11	2.68±0.37	NP
Dorsal cortex	4	1.23±0.11	1.10±0.11**(↓11)	1.16±0.09	NP
Piriform cortex	4	1.13±0.09	0.99±0.09**(↓12)	1.07±0.07	NP
Corpus callosum	4	0.37±0.06	0.37±0.05	0.37±0.04	NP
Thalamus - Height	4	5.06±0.32	4.62±0.28**(↓9)	5.13±0.39	NP
Thalamus - Width	4	8.02±0.34	7.49±0.35**(↓7)	8.09±0.52	NP
Thalamus/cortex – Overall width	4	13.36±0.54	12.80±0.56	13.73±0.95	NP
Hippocampus – Length from midline	4	3.05±0.27	3.17±0.25	3.16±0.19	NP
Hippocampus – With dentate gyrus	4	0.56±0.04	0.51±0.03*(↓9)	0.55±0.04	NP
Hippocampus – Length dentate gyrus	4	1.45±0.12	1.32±0.11	1.54±0.18	NP
Dorsal cortex	5	1.33±0.06	1.21±0.11**(↓9)	1.31±0.10	NP
Piriform cortex	5	1.16±0.09	1.02±0.09**(↓12)	1.13±0.09	NP
Thalamus - Width	5	7.63±0.26	6.93±0.35**(↓9)	7.55±0.28	NP
Hippocampus – With dentate gyrus	5	0.65±0.03	0.60±0.05*(↓8)	0.66±0.05	NP
Hippocampus – Width overall	5	1.45±0.08	1.26±0.09**(↓13)	1.44±0.09	NP
Cerebellum – Height		5.28±0.34	4.63±0.32**(↓12)	5.08±0.35	NP
Cerebellum – Length		6.36±0.44	5.96±0.24	6.48±0.45	NP
Cerebellum – Preculminate fissure – Inner granular layer		145±21	114±15**(↓21)	135±25	NP
Cerebellum – Preculminate fissure – Molecular layer		199.5±21.9	175.7±21.7**(↓12)	198.7±15.0	NP
Cerebellum – Prepyramidal fissure – Inner granular layer		132±13	95±18**(↓28)	138±21	NP
Cerebellum – Prepyramidal fissure – Molecular layer		191.8±15.9	159.9±17.3**(↓17)	196.8±13.8	NP

a Data were obtained from Table 34 on pages 187-191 of the study report; n=6-12. Percent difference from controls (calculated by reviewers) is presented parenthetically.
NP Data not provided
* Statistically different from control, $p \leq 0.05$
** Statistically different from control, $p \leq 0.01$

III. DISCUSSION and CONCLUSIONS

A. <u>INVESTIGATORS' CONCLUSIONS</u>: The investigators concluded that a dose of 0.40 mg/kg/day was toxic to the offspring following maternal exposure and resulted in the premature termination of the selected offspring in this group. All dose levels were associated with higher maternal body weight and food consumption during gestation. The 0.12 and 0.20 mg/kg/day F1 groups had slightly decreased bodyweights post-weaning with an associated slight delay in the time of vaginal opening. No effect on the function or morphology of the nervous system was observed. The NOAEL for developmental neurotoxicity was 0.20 mg/kg/day.

B. REVIEWER'S COMMENTS

1. **Maternal toxicity:** There were no effects of treatment on mortality, clinical signs, body weights, body weight gains, food consumption, functional observational battery parameters, reproductive performance, or gestation length.

   Three control dams (Nos. 17, 18, and 20) were sacrificed on LD 2 due to clinical signs (piloerection, hunched posture, pinched in sides, facial staining, vaginal bleeding, and signs of diarrhea). These animals had littered on GD 23. One 0.12 mg/kg/day female was found dead on LD 24. There were no changes in clinical condition observed prior to death and no evidence of a treatment-related effect. One 0.12 mg/kg/day female and two 0.40 mg/kg/day females were sacrificed on GD 25 because they had failed to litter. All three animals were found not to have been pregnant.

   The maternal LOAEL was not observed. The maternal NOAEL is 0.4 mg/kg/day.

2. **Offspring toxicity:** Following culling on PND 5, mortality and associated clinical signs of toxicity were observed in the 0.40 mg/kg/day pups. A total of 32 males and 27 females were missing and presumed dead, found dead, or killed for humane reasons or due to clinical signs of toxicity. The pups were generally small in size and presented with dehydration (133-151 observations in 42-45 pups) and tremors (276-292 observations in 66-67 pups). Additionally at this dose, offspring body weights were decreased ($p \leq 0.05$) by 10-36% compared to controls from PND 8 to 36. There were no surviving pups at this dose level after PND 38. Since these deaths left an insufficient number of pups to complete all of the study objectives, all dams and pups at this dose were removed from the study during PND 15-38.

   No treatment-related effects were observed on litter parameters (number born live, number born dead, sex ratio (% male), mean litter size, live birth index, and viability index), clinical signs, FOB parameters, motor activity, auditory startle reflex, learning and memory, sexual maturation, brain weight, or gross or microscopic pathology in the 0.12 or 0.2 mg/kg/day groups.

   Decreases ($p \leq 05$) in post-weaning body weight were observed in the 0.12 and 0.20 mg/kg/day males throughout the post-weaning interval (PND 36-63), but these reductions were slight and appeared to have reached the bottom of the dose response curve. The pup body weight data were evaluated with the Mixed Model Analysis which is specifically developed to analyzed the body weight data derived from DNT studies; the results demonstrated that there were statistically significant reductions in 0.12 and 0.20 mg/kg males, but the decreases were 6% and 3% relative to the controls in 0.20 and 0.12 mg/kg/day males, respectively. In females, the decreases were 4% and 3% in 0.2 and 0.12 mg/kg/day groups, respectively and were not statistically significant. It was determined that the decrease in 0.12 mg/kg/day was marginal and the magnitude of decrease was considered not to be biological significant. Therefore, the offspring NOAEL was 0.12 mg/kg/day, and the offspring LOAEL was 0.20 mg/kg/day.

This study is classified as acceptable/non-guideline.

C. **STUDY DEFICIENCIES:** The following minor deficiencies were noted but do not alter the conclusions of this report:

- Positive control data for neurotoxicity testing were not provided.
- Stability data of the compound in the vehicle were not provided.
- In-life dates were not reported.
- Details concerning the methodology of the functional observational battery, motor activity, auditory startle reflex, and learning and memory testing were not provided.

ATTACHMENT

The following are pages 129 through 136 of the study report.

TABLE 22 Intergroup Comparison Of Motor Activity Day 14 - F1 Animals

MALES		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.2
Minutes 1-5	Mean	44.7	55.4	38.0
	S.D.	23.7	31.2	33.1
	N	10	11	12
Minutes 6-10	Mean	24.9	30.0	21.1
	S.D.	28.4	23.7	26.7
	N	10	11	12
Minutes 11-15	Mean	24.3	19.7	30.3
	S.D.	33.8	23.6	26.1
	N	10	11	12
Minutes 16-20	Mean	22.3	17.2	29.3
	S.D.	24.6	27.1	29.3
	N	10	11	12
Minutes 21-25	Mean	24.8	17.5	27.4
	S.D.	24.2	21.2	37.6
	N	10	11	12
Minutes 26-30	Mean	19.9	5.1	14.4
	S.D.	16.2	5.9	27.1
	N	10	11	12
Minutes 31-35	Mean	15.8	10.1	20.7
	S.D.	29.0	16.4	27.7
	N	10	11	12
Minutes 36-40	Mean	17.8	13.0	15.4
	S.D.	22.1	24.9	24.5
	N	10	11	12
Minutes 41-45	Mean	15.4	17.9	4.9
	S.D.	27.7	28.3	10.1
	N	10	11	12
Minutes 46-50	Mean	12.3	15.3	4.4
	S.D.	17.2	22.1	7.1
	N	10	11	12
Overall (1-50)	Mean	222.2	201.1	205.8
	S.D.	107.8	118.0	155.0
	N	10	11	12

TABLE 22 Intergroup Comparison Of Motor Activity Day 14 - F1 Animals

FEMALES		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.2
Minutes 1-5	Mean	21.6	29.5	45.4* ↑ 110
	S.D.	13.1	23.0	25.5
	N	9	10	11
Minutes 6-10	Mean	17.7	25.5	25.5
	S.D.	22.4	25.7	26.1
	N	9	10	11
Minutes 11-15	Mean	12.9	33.0* ↑ 156	3.5
	S.D.	25.7	26.5	3.2
	N	9	10	11
Minutes 16-20	Mean	21.2	7.9	13.3
	S.D.	22.4	15.0	29.6
	N	9	10	11
Minutes 21-25	Mean	22.8	5.5	19.4
	S.D.	20.9	6.6	28.6
	N	9	10	11
Minutes 26-30	Mean	13.8	9.7	13.5
	S.D.	23.3	14.1	22.9
	N	9	10	11
Minutes 31-35	Mean	9.6	12.2	8.1
	S.D.	16.4	17.8	13.7
	N	9	10	11
Minutes 36-40	Mean	8.6	13.8	6.1
	S.D.	17.7	21.4	12.1
	N	9	10	11
Minutes 41-45	Mean	14.7	14.5	9.7
	S.D.	25.9	21.4	12.3
	N	9	10	11
Minutes 46-50	Mean	13.2	9.8	3.8
	S.D.	24.5	14.9	3.7
	N	9	10	11
Overall (1-50)	Mean	155.9	161.4	148.2
	S.D.	145.7	101.9	107.9
	N	9	10	11

TABLE 23 Intergroup Comparison Of Motor Activity Day 18 - F1 Animals

MALES		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.2
Minutes 1-5	Mean	50.8	38.2	45.5
	S.D.	27.6	32.2	30.2
	N	10	11	12
Minutes 6-10	Mean	44.0	45.8	46.5
	S.D.	29.8	32.1	33.4
	N	10	11	12
Minutes 11-15	Mean	33.0	36.0	33.2
	S.D.	30.0	34.3	32.0
	N	10	11	12
Minutes 16-20	Mean	32.6	35.3	22.3
	S.D.	34.8	35.9	27.4
	N	10	11	12
Minutes 21-25	Mean	23.4	35.2	31.2
	S.D.	24.7	37.2	33.2
	N	10	11	12
Minutes 26-30	Mean	20.9	32.1	19.9
	S.D.	32.0	35.4	26.8
	N	10	11	12
Minutes 31-35	Mean	18.2	30.3	21.6
	S.D.	21.9	33.0	27.2
	N	10	11	12
Minutes 36-40	Mean	18.1	30.3	20.2
	S.D.	29.6	31.2	25.5
	N	10	11	12
Minutes 41-45	Mean	18.6	39.3	21.5
	S.D.	29.0	38.7	28.2
	N	10	11	12
Minutes 46-50	Mean	25.7	29.4	13.3
	S.D.	30.3	30.7	22.7
	N	10	11	12
Overall (1-50)	Mean	285.3	351.7	275.0
	S.D.	154.4	276.7	180.7
	N	10	11	12

TABLE 23 Intergroup Comparison Of Motor Activity Day 18 - F1 Animals

FEMALES		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.2
Minutes 1-5	Mean	22.9	52.8* ↑131	54.3** ↑137
	S.D.	14.7	23.2	30.3
	N	9	10	11
Minutes 6-10	Mean	25.3	41.3	47.5* ↑88
	S.D.	19.4	20.7	29.0
	N	9	10	11
Minutes 11-15	Mean	17.9	31.6	25.7
	S.D.	22.5	28.2	24.8
	N	9	10	11
Minutes 16-20	Mean	26.6	27.4	16.5
	S.D.	20.1	27.5	28.3
	N	9	10	11
Minutes 21-25	Mean	32.1	20.6	19.9
	S.D.	29.8	25.0	29.0
	N	9	10	11
Minutes 26-30	Mean	29.2	27.0	17.1
	S.D.	26.1	24.0	29.4
	N	9	10	11
Minutes 31-35	Mean	29.6	28.6	27.7
	S.D.	28.2	32.2	23.5
	N	9	10	11
Minutes 36-40	Mean	24.1	18.7	28.2
	S.D.	24.0	23.2	26.7
	N	9	10	11
Minutes 41-45	Mean	20.9	12.8	22.5
	S.D.	29.7	25.2	21.0
	N	9	10	11
Minutes 46-50	Mean	17.3	20.7	19.5
	S.D.	26.3	25.8	24.3
	N	9	10	11
Overall (1-50)	Mean	245.9	281.5	279.0
	S.D.	147.6	162.8	185.4
	N	9	10	11

TABLE 24 Intergroup Comparison Of Motor Activity Day 22 - F1 Animals

MALES		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.2
Minutes 1-5	Mean	67.3	59.8	60.0
	S.D.	12.9	25.0	28.1
	N	10	11	12
Minutes 6-10	Mean	65.2	52.5	66.9
	S.D.	16.5	17.2	23.1
	N	10	11	12
Minutes 11-15	Mean	41.3	41.0	38.6
	S.D.	27.4	34.0	22.8
	N	10	11	12
Minutes 16-20	Mean	44.2	33.7	28.3
	S.D.	27.0	26.8	31.9
	N	10	11	12
Minutes 21-25	Mean	42.6	34.0	44.1
	S.D.	28.8	27.4	37.6
	N	10	11	12
Minutes 26-30	Mean	41.3	30.1	43.2
	S.D.	27.9	31.1	28.5
	N	10	11	12
Minutes 31-35	Mean	51.4	33.6	44.1
	S.D.	35.2	31.0	33.3
	N	10	11	12
Minutes 36-40	Mean	52.7	24.5* ↓54	64.9
	S.D.	30.2	29.3	32.0
	N	10	11	12
Minutes 41-45	Mean	43.4	32.0	49.5
	S.D.	28.6	25.7	25.4
	N	10	11	12
Minutes 46-50	Mean	35.0	31.1	47.7
	S.D.	32.4	25.7	29.4
	N	10	11	12
Overall (1-50)	Mean	484.4	372.4	487.3
	S.D.	148.5	185.7	206.6
	N	10	11	12

TABLE 24 Intergroup Comparison Of Motor Activity Day 22 - F1 Animals

FEMALES		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.2
Minutes 1-5	Mean	60.8	70.5	73.4
	S.D.	13.5	15.5	20.3
	N	9	10	11
Minutes 6-10	Mean	52.6	55.9	66.3
	S.D.	19.8	22.5	22.5
	N	9	10	11
Minutes 11-15	Mean	43.2	47.0	49.3
	S.D.	27.3	28.2	27.5
	N	9	10	11
Minutes 16-20	Mean	43.0	52.6	48.6
	S.D.	34.0	27.2	32.1
	N	9	10	11
Minutes 21-25	Mean	35.1	44.7	47.6
	S.D.	25.4	32.7	25.0
	N	9	10	11
Minutes 26-30	Mean	26.3	51.5* ↑96	48.3
	S.D.	23.2	25.6	28.2
	N	9	10	11
Minutes 31-35	Mean	20.1	45.3* ↑125	54.7** ↑172
	S.D.	26.6	27.7	23.6
	N	9	10	11
Minutes 36-40	Mean	26.1	48.9	40.0
	S.D.	26.4	28.1	23.7
	N	9	10	11
Minutes 41-45	Mean	37.7	43.9	40.8
	S.D.	28.7	30.2	23.7
	N	9	10	11
Minutes 46-50	Mean	35.6	27.1	37.8
	S.D.	35.7	26.4	29.7
	N	9	10	11
Overall (1-50)	Mean	380.4	487.4	506.8
	S.D.	158.9	170.4	203.5
	N	9	10	11

TABLE 25 Intergroup Comparison Of Motor Activity Day 60 - F1 Animals

MALES		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.2
Minutes 1-5	Mean	74.9	66.0* ↓12	71.9
	S.D.	8.2	10.3	8.6
	N	10	11	12
Minutes 6-10	Mean	70.7	65.3	67.8
	S.D.	9.8	14.5	9.8
	N	10	11	12
Minutes 11-15	Mean	69.4	66.4	76.3
	S.D.	9.7	14.7	14.1
	N	10	11	12
Minutes 16-20	Mean	67.3	62.7	69.0
	S.D.	11.2	14.0	19.5
	N	10	11	12
Minutes 21-25	Mean	61.7	55.8	62.8
	S.D.	21.3	27.2	17.7
	N	10	11	12
Minutes 26-30	Mean	50.0	51.5	52.1
	S.D.	26.4	26.3	21.5
	N	10	11	12
Minutes 31-35	Mean	49.8	41.5	36.9
	S.D.	35.0	28.4	25.6
	N	10	11	12
Minutes 36-40	Mean	55.1	32.7	36.8
	S.D.	19.5	29.2	32.9
	N	10	11	12
Minutes 41-45	Mean	50.6	32.0	24.3* ↓52
	S.D.	27.7	30.3	24.5
	N	10	11	12
Minutes 46-50	Mean	43.2	27.4	32.2
	S.D.	33.9	36.2	29.1
	N	10	11	12
Overall (1-50)	Mean	592.7	501.3	530.0
	S.D.	133.7	139.1	129.7
	N	10	11	12

TABLE 25 Intergroup Comparison Of Motor Activity Day 60 - F1 Animals

FEMALES		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.2
Minutes 1-5	Mean	66.8	60.6	59.3
	S.D.	12.1	11.4	10.6
	N	9	10	11
Minutes 6-10	Mean	65.0	66.1	59.8
	S.D.	9.0	9.9	14.4
	N	9	10	11
Minutes 11-15	Mean	60.1	62.6	60.2
	S.D.	7.9	7.6	10.7
	N	9	10	11
Minutes 16-20	Mean	61.7	63.9	58.5
	S.D.	11.2	18.4	19.3
	N	9	10	11
Minutes 21-25	Mean	65.2	55.4	49.8
	S.D.	12.8	24.4	21.8
	N	9	10	11
Minutes 26-30	Mean	51.2	48.2	45.5
	S.D.	14.8	20.5	23.6
	N	9	10	11
Minutes 31-35	Mean	48.6	49.9	46.5
	S.D.	20.6	19.4	19.7
	N	9	10	11
Minutes 36-40	Mean	54.4	45.6	54.7
	S.D.	25.1	25.4	23.1
	N	9	10	11
Minutes 41-45	Mean	52.6	44.9	56.3
	S.D.	22.0	23.5	26.5
	N	9	10	11
Minutes 46-50	Mean	53.3	59.7	55.4
	S.D.	25.1	16.9	29.3
	N	9	10	11
Overall (1-50)	Mean	578.9	556.9	545.9
	S.D.	125.6	109.8	130.0
	N	9	10	11

13544

R180178

Chemical Name: Abamectin

PC Code: 122804
HED File Code: 13000 Tox Reviews
Memo Date: 1/6/2010
File ID: 00000000
Accession #: 000-00-0134

HED Records Reference Center
1/13/2010